

# Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Chari A, Vogl DT, Gavriatopoulou M, et al. Oral selinexor–dexamethasone for triple-class refractory multiple myeloma. *N Engl J Med* 2019;381:727-38. DOI: 10.1056/NEJMoa1903455

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<b>Clinical Study Protocol</b> <b>KCP-330-012</b> <b>A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) plus Low-Dose Dexamethasone in Patients with Multiple Myeloma Quad-refractory to Previous Therapies</b> <b>Study Name: STORM (Selinexor Treatment of Refractory Myeloma)</b>	
<b>Drug Development Phase:</b>	Phase 2b
<b>Investigational Product:</b>	Selinexor (KPT-330)
<b>Indication:</b>	Multiple myeloma quad-refractory to prior treatment with bortezomib, carfilzomib, lenalidomide, and pomalidomide
<b>Sponsor:</b>	Karyopharm Therapeutics, Inc. 85 Wells Avenue Newton, MA 02459 USA Tel. + (617) 658-0600
<b>Protocol Date and Version:</b>	24 December 2014, Version 1.0
<b>CONDUCT</b>  In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.	
<b>CONFIDENTIAL INFORMATION</b>  This document is the sole property of Karyopharm Therapeutics, Inc. (Karyopharm). This document and any and all information contained herein has to be considered and treated as strictly confidential. This document shall be used only for the purpose of the disclosure herein provided. No disclosure or publication shall be made without the prior written consent of Karyopharm.	

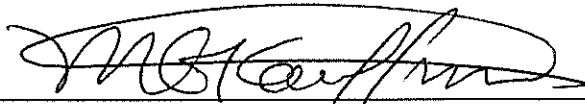
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## PROTOCOL APPROVAL SIGNATURE PAGE

### SPONSOR: KARYOPHARM THERAPEUTICS, INC.

I have read and understand the contents of this clinical protocol for Study No. KCP-330-012 dated 24 Dec 2014 and agree to meet all obligations of Karyopharm Therapeutics, Inc., as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other Investigators of all relevant information that becomes available during the conduct of this Study.

Approved By:



Michael Kauffman, MD, PhD  
Acting Chief Medical Officer  
Karyopharm Therapeutics, Inc.

29 Dec 2014

Date



Sharon Shacham, PhD  
President and Chief Scientific Officer  
Karyopharm Therapeutics, Inc.

29 Dec 2014

Date

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## PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Study No. KCP-330-012 dated 24 Dec 2014 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the Study in accordance with current Good Clinical Practices, ICH E6, and applicable FDA regulatory requirements:

**Name of Principal Investigator:**

**Principal Investigator's Signature:** \_\_\_\_\_

**Principal Investigator's Name:** \_\_\_\_\_

**Institution:** \_\_\_\_\_

**Date:** \_\_\_\_\_

## PROTOCOL SYNOPSIS

Sponsor: Karyopharm Therapeutics, Inc.	Investigational Product: Selinexor (KPT-330)	Developmental Phase: Phase 2b
<b>Title of Study:</b> A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) plus Low-Dose Dexamethasone in Patients with Multiple Myeloma Quad-refractory to Prior Therapies		
<b>Protocol Number:</b> KCP-330-012: STORM (Selinexor Treatment of Refractory Myeloma)		
<b>Indication:</b> Multiple myeloma quad-refractory to prior therapies (bortezomib, carfilzomib, lenalidomide, and pomalidomide)		
<b>Objectives:</b> <u>Primary Objectives:</u> <ul style="list-style-type: none"> <li>Determine the Overall Response Rate (ORR), including Partial Response (PR), Very Good Partial Response (VGPR), Complete Response (CR), and stringent complete response (sCR) to selinexor 80 mg + low-dose dexamethasone (20 mg) in patients with MM whose disease is quad-refractory to prior therapies (bortezomib, lenalidomide, carfilzomib, and pomalidomide)</li> <li>Evaluate the efficacy of selinexor + dexamethasone in comparison to a minimally effective lower threshold level of ORR</li> </ul> <u>Secondary Objectives:</u> <ul style="list-style-type: none"> <li>Determine Duration of Response (DOR = the duration of time measured from when measurement criteria for response were first met until the date of first recurrence, PD or death)</li> <li>Determine the Clinical Benefit Rate (CBR = sCR + CR + PR + Minor Response [MR]), and duration of CBR</li> <li>Determine the Disease Control Rate (DCR = CBR + stable disease [SD; for a minimum of 12 weeks]), as well as duration of DCR</li> <li>Determine Progression Free Survival (PFS)</li> <li>Compare time to progression (TTP) obtained with Sel-Dex versus the patient's TTP(s) on prior therapy(ies) for MM</li> <li>Determine the Overall Survival (OS) of patients with quad-refractory MM treated with Sel-Dex.</li> <li>Compare PFS, ORR, DOR, DCR, and OS obtained with Sel-Dex in patients with International Staging System (ISS) stage III versus ISS stage I or II</li> <li>Assess ORR, DOR, CBR, disease control and PFS in the sub-group of patients (<math>\geq 25\%</math>) with penta-refractory MM (bortezomib, lenalidomide, carfilzomib, and pomalidomide and an anti-CD38 MAb [e.g., SAR 650984 or daratumumab])</li> </ul>		

Sponsor: Karyopharm Therapeutics, Inc.	Investigational Product: Selinexor (KPT-330)	Developmental Phase: Phase 2b
<ul style="list-style-type: none"> <li>Assess Quality of Life using the Functional Assessment of Cancer Therapy - Multiple Myeloma (FACT-MM)</li> </ul> <p><b><u>Exploratory Objectives:</u></b></p> <ul style="list-style-type: none"> <li>Compare ORR, DOR, PFS, and OS in patients with free light chain (FLC) MM treated with selinexor + dexamethasone</li> <li>Assess ORR, DOR, PFS, and OS in patients receiving dose increases during the study</li> <li>Correlational studies to evaluate response as related to: <ul style="list-style-type: none"> <li>Cytogenetic and fluorescent <i>in situ</i> hybridization (FISH) prognostic markers including p53 abnormalities and chromosomal aberrations (e.g., del 17p, t(4;14), t(14;16), del 13) and other MM cytogenetic classifications</li> <li>Gene expression and plasma protein levels</li> <li>Time since initial diagnosis of active myeloma</li> <li>Lytic lesions as measured by skeletal survey</li> </ul> </li> </ul>		
<p><b>Background and Study Rationale</b></p> <p>Multiple myeloma (MM) is the second most common hematological malignancy (after non-Hodgkin's lymphoma), representing 1% of all cancers and 2% of all cancer deaths. Despite the increased effectiveness of a variety of agents, nearly all patients will eventually relapse with their disease becoming drug-resistant. With over 15,000 deaths from MM anticipated in 2014, there is an unmet medical need for therapies in patients with relapsed and/or refractory MM that has progressed on available agents.</p> <p>Selinexor is an orally bioavailable, selective inhibitor of nuclear export (SINE) compound that specifically blocks exportin 1 (XPO1). Selinexor and other SINE compounds have demonstrated anti-MM activity in preclinical studies and in an ongoing Phase 1 clinical study, both as a single agent and in combination with dexamethasone.</p> <p>In a Phase 1 clinical trial (KCP-330-001) of selinexor in patients with advanced hematological malignancies, patients with heavily pretreated MM were treated with either single-agent selinexor or selinexor in combination with low-dose (20 mg) dexamethasone, both dosed twice weekly. As of 15 Dec 2014, of 44 patients enrolled, 34 patients had received single-agent selinexor and 10 patients were treated with selinexor 45 mg/m<sup>2</sup> (~80 mg) plus dexamethasone. Higher doses of selinexor (60 mg/m<sup>2</sup>) with 20 mg dexamethasone were not well tolerated in this patient population. Among the 34 patients receiving single-agent selinexor therapy, including 6 patients who were non-evaluable, best responses included one PR (3%), five MRs (15%), 16 SDs (47%), and six PDs (18%). The clinical benefit response rate (CBR=sCR+PR+MR) was 18%. Some patients treated with single-agent selinexor also received very low doses of dexamethasone (up to 12 mg with each dose of selinexor) or another glucocorticoid as part of supportive care.</p> <p>Ten patients were treated with 45 mg/m<sup>2</sup> (~80 mg) of oral selinexor and 20 mg of dexamethasone, each dosed twice weekly. All of these patients had MM refractory to their most recent therapy and at least one proteasome inhibitor and one immunomodulatory drug</p>		

Sponsor: Karyopharm Therapeutics, Inc.	Investigational Product: Selinexor (KPT-330)	Developmental Phase: Phase 2b
<p>(IMiD), as well as to glucocorticoids (which were given with nearly every prior anti-MM regimen), and many of the patients had quad-refractory MM. The best responses among the nine evaluable patients were one stringent complete response (sCR) (11%), five PRs (55%), two MR (22%), one SD (11%), one PD (11%); one patient was not evaluable (NE) for response (10%). The CBR was 88% and the ORR was 66%. Several of these responses were durable for &gt; 6 months, without clinically significant cumulative toxicities.</p> <p>These data provide the rationale for the evaluation of selinexor plus low-dose dexamethasone in heavily pretreated patients with MM in this Phase 2b study.</p>		
<p><b>Methodology:</b></p> <p>This is a Phase 2b, single-arm, open-label, multicenter study of selinexor (80 mg) with low-dose (20 mg) dexamethasone given orally to patients with heavily pretreated MM quad-refractory to bortezomib, carfilzomib, lenalidomide, and pomalidomide</p>		
<p><b>Diagnosis and Main Criteria for Inclusion:</b></p> <p>Male and female patients, ages <math>\geq 18</math> years, with measurable progressive MM according to the International Myeloma Working Group (IMWG) Uniform Response Criteria. Patients must have received <math>\geq 3</math> prior regimens including (alone or in combination) an alkylating agent, bortezomib, carfilzomib, lenalidomide, pomalidomide, and a glucocorticoid, and that their MM is quad-refractory to previous therapies, and was refractory to their most recent therapy. Refractory is defined as <math>\leq 25\%</math> response to therapy, progression during therapy, or progression within 60 days after completion of therapy. At least 25% of the patients included must have MM refractory to an anti-CD38 monoclonal antibody therapy.</p>		
<p><b>Test Product, Dose and Mode of Administration:</b></p> <p>Selinexor will be given at an oral fixed milligram (mg) dose of 80 mg twice weekly for 3 weeks per 4-week cycle (total of 6 selinexor doses per cycle). Selinexor will not be administered during Week 4.</p> <p>Dexamethasone (20 mg) will be given with each dose of selinexor during Weeks 1-3 and alone during Week 4 of every 4-week cycle at the same dose schedule used in Weeks 1-3. For patients with partial intolerance to glucocorticoids (as determined by the investigator), a minimum dose of 10 mg dexamethasone is permitted.</p> <p>In select cases (e.g., for patients showing SD or PR and tolerating treatment particularly well), the selinexor dose may be increased by 20 mg (i.e., to 100 mg twice weekly) after consultation with the medical monitor. The dose level for an individual patient may be escalated based on efficacy considerations after completing a minimum of 2 cycles of study therapy. However, in no case may the dose for a given patient exceed 70 mg/m<sup>2</sup>.</p>		



Sponsor: Karyopharm Therapeutics, Inc.	Investigational Product: Selinexor (KPT-330)	Developmental Phase: Phase 2b
<b>Concomitant Medications:</b> To minimize nausea, unless contraindicated, all patients must receive 5-HT3 antagonists (e.g., ondansetron 8 mg or equivalent) starting on Day 1 before the first dose of selinexor and continued 2-3 times daily, as needed. Additional anti-nausea and anti-anorexia agents may be given as needed ( <sup>1</sup> per National Comprehensive Cancer Network® [NCCN] Clinical Practice Guidelines® for Antiemesis and NCCN Clinical Practice Guidelines® for Palliative Care). Patients will also receive therapy as needed to mitigate selinexor side effects, as part of best supportive care (BSC), including blood product transfusions, antimicrobials, and (as appropriate) growth factors including granulocyte colony-stimulating factors for neutropenia, erythropoietins for anemia, and/or platelet-stimulating factors for thrombocytopenia. Patients may continue their baseline medication(s). Medications to treat concomitant diseases like diabetes, hypertension, etc., are allowed. Patients will also receive concomitant medications that are medically necessary as standard care to treat symptoms, AEs and intercurrent illnesses. Patients may receive red blood cell or platelet transfusions, if clinically indicated, per institutional guidelines. Acetaminophen on days of selinexor dosing will not exceed a total daily dose of 1 gram. Concurrent therapy with growth factors is allowed. Concurrent therapy with any other approved or investigational anti-cancer therapy is not allowed. Other investigational agents should not be used during the study.		
<b>Study Numbers:</b> Approximately 80 patients with heavily pretreated, quad-refractory MM who meet all eligibility criteria and no exclusion criteria will be enrolled.		
<b>Study Duration:</b> The enrollment period for this study is expected to be approximately 15 months. There is no maximum treatment duration for the study, patients will receive treatment until progression or intolerability occurs.		
<b>Criteria for Evaluation:</b> <u>Safety:</u> Safety and tolerability will be evaluated by means of AE reports, physical examinations, and laboratory safety evaluations. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 will be used for grading of AEs. For all AEs, investigators will provide their assessment of causality as 1) unrelated, 2) possibly related, or 3) related.		

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Sponsor: Karyopharm Therapeutics, Inc.	Investigational Product: Selinexor (KPT-330)	Developmental Phase: Phase 2b
<p><b>Efficacy:</b></p> <p><i>Primary:</i> Overall Response Rate (ORR), with supportive information obtained from the duration of ORR (DOR), to evaluate the efficacy of selinexor plus dexamethasone in comparison to a minimally effective lower threshold level of ORR (i.e., 15%) in patients with quad-refractory MM.</p> <p><i>Secondary:</i></p> <ul style="list-style-type: none"> <li>• DOR</li> <li>• CBR, with supportive information from duration of CBR</li> <li>• DCR, with supportive information from duration of DCR</li> <li>• PFS</li> <li>• OS</li> <li>• TTP on Sel-Dex vs. TTP on most recent therapy</li> <li>• ORR, DOR, CBR, OS, disease control and PFS in the sub-group of patients (25%) with penta-refractory MM</li> <li>• QoL using the FACT-MM Questionnaire</li> </ul> <p><b>PK and PD:</b></p> <ul style="list-style-type: none"> <li>• PK properties of selinexor in patients with quad-refractory MM</li> <li>• PDn changes in selected markers following treatment</li> </ul>		
<p><b>Criteria for Treatment Discontinuation:</b></p> <p>At the discretion of the investigator, the investigator may remove a patient from study treatment at his/her discretion for any of the following reasons:</p> <ul style="list-style-type: none"> <li>• Disease progression</li> <li>• Unacceptable AE(s) or failure to tolerate the study treatment</li> <li>• Patient decides to discontinue study therapy and withdraws consent</li> </ul> <p>Any medically appropriate reason or significant protocol violation, in the opinion of the investigator.</p> <p>Patients may decide to discontinue study treatment for any reason. Patients who elect to discontinue study treatment should be encouraged to continue in the study so that follow-up information on disease progression and survival status may be obtained. However, patients may elect to withdraw consent and decline further participation in the study.</p>		
<p><b>Statistical Methods:</b></p> <p>The sample size for this study addresses the primary study objective of evaluating the clinical effect of selinexor plus dexamethasone by reference to a minimal threshold level for ORR, set to 0.15 (15%).</p> <p>Based on preliminary evidence from an ongoing Phase 1 trial (KCP-330-001), it is believed that selinexor + dexamethasone may exhibit substantial efficacy; therefore, the statistical</p>		

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<p>test associated with the comparison to the threshold will maintain a Type I error rate of 0.025, one-sided.</p> <p>A sample size of 72 patients will allow a one-sided test at <math>\alpha=0.025</math> to detect an ORR of <math>\geq 0.30</math> against the threshold ORR of 0.15, with 90% power. Up to 10% additional patients may be enrolled to account for potential drop-outs, therefore approximately 80 patients will be enrolled in this study.</p> <p>The primary statistical analysis of efficacy will be performed on ORR (achievement of sCR, CR, VGPR, or PR) for the overall evaluable population with supportive data provided by DOR; it is anticipated that DOR may be on the order of 5-7 months or more following initial documentation of response. The modified intent-to-treat (mITT) population will be taken as the set of patients who received at least one dose of study treatment.</p> <p>Quality of life (QoL) will be assessed using the FACT-MM. This instrument combines the general version of the Functional Assessment of Cancer Therapy (FACT-G) with a MM-specific subscale (14 items). The trial outcomes index (TOI; total of 41 items) will be the primary measurement of interest, comprised of the physical and functional subscales plus the MM-specific subscale.</p> <p>Safety analyses will be performed on the overall population of patients who received at least one dose of study treatment. The safety and tolerability of study treatment will be evaluated by means of drug-related AE reports, physical examinations, and laboratory safety evaluations. The NCI CTCAE v.4.03 will be used for grading of AEs. Investigators will provide their assessment of causality for all AEs as 1) not related, 2) possibly related, or 3) related. Laboratory data will be evaluated for changes from baseline as well as for shifts from baseline relative to CTCAE criteria for abnormal values.</p>		

**Table 1.1 Schedule of Assessments and Study Activities**

Activity/Assessment	Screening	Cycle 1				Cycles $\geq 2$		End-of-Treatment (EoT) Visit	Survival Follow-up <sup>27</sup> (Every 3 mo.)
	Day -14 to Day -1	Day 1	Day 3 <sup>26</sup>	Day 8	Day 15	Day 1	Day 15	30 Days Post-Last Dose	
		$\pm 1$ day				$\pm 2$ days		$\pm 7$ days	$\pm 14$ days
Informed consent <sup>1</sup>	X								
Inclusion/exclusion criteria	X								
Demographics	X								
Medical history <sup>2</sup>	X	X							
Randomization (Day -3 to -1) <sup>3</sup>	X								
Patient height	X								
Patient weight	X	X		X	X	X		X	
Body Surface Area (BSA) <sup>4</sup>	X								
Vital signs <sup>5</sup>	X	X		X	X	X		X	
Physical examination, full <sup>6</sup>	X							X	
Physical examination, limited <sup>6</sup>		X		X	X	X			
ECOG <sup>7</sup>		X				X		X	
Echocardiogram or Multiple Gated Acquisition (MUGA) scan <sup>8</sup>	X							X	
Ophthalmologic exam <sup>9</sup>	X							X	
Oxygen saturation <sup>10</sup>		X							
12-lead ECG <sup>11</sup>	X							X	
Urinalysis <sup>12</sup>	X	X				X		X	
CBC with differential <sup>13</sup>	X	X				X		X	

Activity/Assessment	Screening	Cycle 1				Cycles $\geq 2$		End-of-Treatment (EoT) Visit	Survival Follow-up <sup>27</sup> (Every 3 mo.)
	Day -14 to Day -1	Day 1	Day 3 <sup>26</sup>	Day 8	Day 15	Day 1	Day 15	30 Days Post-Last Dose	
		$\pm 1$ day				$\pm 2$ days		$\pm 7$ days	$\pm 14$ days
Thyroid stimulating hormone (TSH)	X							X	
Complete serum chemistry <sup>14</sup>	X	X				X		X	
Limited serum chemistry <sup>15</sup>				X	X		X		
Coagulation tests <sup>16</sup>	X						X	X	
Serum Protein Electrophoresis (SPEP) <sup>17,18</sup>	X					X		X	
24-Hour Urine Protein Electrophoresis (UPEP) <sup>17, 18</sup>	X					X		X	
Free Light Chain (FLC) <sup>17, 18</sup>	X	X			X	X		X	
$\beta$ 2-microglobulin and quantitative Ig levels <sup>19</sup>	X					X			
Skeletal Survey <sup>20</sup>	X					X			
C-reactive protein <sup>21</sup>		X				X			
Serum pregnancy test <sup>22</sup>	X							X	
Bone marrow biopsy and aspirate <sup>23</sup>	X					X			
Study drug dosing		Sel-Dex on Days 1, 3, 8, 10, 15 and 17; Dex only on Days 22 and 24							
Blood draw for PDn testing <sup>24</sup>		X				X			
FACT-MM questionnaire <sup>28</sup>	X					X		X	
Adverse events		X	X	X	X	X		X	
Concomitant medication	X	X	X	X	X	X		X	

Activity/Assessment	Screening	Cycle 1				Cycles $\geq 2$		End-of-Treatment (EoT) Visit	Survival Follow-up <sup>27</sup> (Every 3 mo.)
	Day -14 to Day -1	Day 1	Day 3 <sup>26</sup>	Day 8	Day 15	Day 1	Day 15	30 Days Post-Last Dose	
		$\pm 1$ day				$\pm 2$ days		$\pm 7$ days	$\pm 14$ days
Nutritional consultation <sup>25</sup>	X								
Telephone contact <sup>26</sup>			X						
Antineoplastic therapy after EoT treatment								X	X

Abbreviations: BSA = body surface area; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoT = End of Treatment (Visit); Ig = immunoglobulin; MM = multiple myeloma, PDn = Pharmacodynamic; PK = Pharmacokinetic; QoL = Quality of Life; SPEP = serum protein electrophoresis; TSH = thyroid stimulating hormone; UPEP = urine protein electrophoresis; MUGA = multiple gated acquisition; CBC = complete blood count; FLC = free light chain.

<sup>1</sup> Prior to the first study-specific measures.

<sup>2</sup> Including details of all prior anti-myeloma therapies. Includes baseline symptoms as well as a detailed history of prior cancer therapies, especially MM therapies, including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness.

<sup>3</sup> Randomization must occur on Days -3 to -1 (i.e., prior to Cycle 1 Day 1).

<sup>4</sup> Body Surface Area (BSA) will be calculated by *Dubois 1916* or *Mosteller 1987* method during screening and prior to any dose escalation. Patients with BSA  $<1.4 \text{ m}^2$  are not allowed to have their dose increased if the resulting dose would be  $> 70 \text{ mg/m}^2$ .

<sup>5</sup> Blood pressure, pulse and temperature, unless these data were obtained as part of vital signs.

<sup>6</sup> Full physical examination (PE) for baseline and EoT visit. Limited PEs during the study should be symptom directed.

<sup>7</sup> ECOG performance status assessments will be done on Day 1 of each Cycle.

<sup>8</sup> Echocardiogram or MUGA scan to assess baseline cardiac function and risk of cardiac dysfunction, including cardiomyopathy, particularly in patients who have received prior anthracycline.

<sup>9</sup> Full ophthalmological examination is required at screening and the final visit, and, if clinically indicated, during the study. Prior to dilation, best corrected visual acuity, slit lamp examination including tonometry, following dilation; funduscopy and slit lamp to document lens clarity – if a cataract is seen during the examination, the cataract will be graded according to the Lens Opacities Classification System (LOCS III) provided in *Appendix 5*.

<sup>10</sup> Pulse oximetry will be performed pre-dose for patients at rest breathing room air at Cycle 1 Day 1 only.

<sup>11</sup> During screening and the EoT visit.

<sup>12</sup> Includes appearance, color, urine bilirubin, glucose, hemoglobin, ketones, pH, protein, specific gravity, and urobilinogen. Microscopy will only be performed if clinically indicated.

<sup>13</sup> CBC with differential includes hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count, WBC differential, RBC count, lymphocytes, monocytes, neutrophils, band neutrophils, eosinophils, basophils, platelets. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated

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- <sup>14</sup> Complete serum chemistry for baseline, Day 1 of each Cycle and EoT visit: include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, LDH, total protein, albumin, amylase, lipase, creatinine kinase, urate, and TSH (Note: TSH is shown in the table as a separate item, but it may be captured as part of serum chemistry. If the total bilirubin concentration is increased  $> 1.5 \times \text{ULN}$ , then total bilirubin should be differentiated into the direct and indirect reacting bilirubin.
- <sup>15</sup> Limited chemistry for Cycle 1 (Days 8 and 15), Cycles 2-5 Day 15 including: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin and LDH
- <sup>16</sup> Includes prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT).
- <sup>17</sup> Disease assessment is by serum M protein, urine M protein, or FLC.
- <sup>18</sup> Day 1 of each Cycle only if relevant.
- <sup>19</sup> To be measured during screening and on Day 1 of odd-numbered cycles starting with Cycle 3 (i.e., Cycles 3, 5, 7, etc.).
- <sup>20</sup> A skeletal survey will be performed during screening (within 7 days prior to starting therapy) and every 2 cycles or as clinically indicated thereafter. To include a lateral radiograph of skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri.
- <sup>21</sup> C-reactive protein will be measured on Day 1 of every cycle.
- <sup>22</sup> For women of childbearing potential; negative serum hCG pregnancy test  $\leq 3$  days of first study dose.
- <sup>23</sup> Bone marrow biopsies will be obtained within 14 days prior to first dose (baseline) on C1 D1 and within 7 days prior to Cycle 2 Day 1 (pre-dose) to assess MM histology. Optional: When possible, a bone marrow aspirate/biopsy should also be obtained at the time of disease progression.
- <sup>24</sup> Blood draws (plasma proteins [2 ml] and whole blood RNA [2.5 ml]) will be collected for PDn analysis on Cycle 1 Day 1 pre-dose and 4 hours post-dose ( $\pm 10$  min)
- <sup>25</sup> It is strongly recommended that patients be given nutritional consultation to discuss food recommendations and strategies for managing potential nausea and appetite changes experienced with selinexor. May be done during Screening or pre-dose on C1 D1.
- <sup>26</sup> ***Telephone call with patient to evaluate supportive care medications and adverse events, and to adjust supportive care as appropriate. The telephone contact with the patient must take place on Day 3 following the Cycle 1 Day 1 selinexor dosing and as needed following that call.***
- <sup>27</sup> After study discontinuation, a telephone call will be made to the patient (or the patient's family) every 3 months to inquire about the patient's MM status, well-being, and information on any antineoplastic therapies utilized since discontinuation of selinexor study treatment.
- <sup>28</sup> QoL questionnaire (FACT-MM; *Appendix 4*) will be completed during screening, on Day 1 of Cycles  $\geq 2$ , and at the EoT visit.

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## LIST OF ABBREVIATIONS

Abbreviation	Definition
Adria	Adriamycin (doxorubicin)
AE	adverse event
ALT	alanine transaminase (SGPT)
AML	acute myeloid leukemia
ANC	absolute neutrophil count
anti-CD38 MAb	monoclonal antibodies against CD38 antigen expressed by leukocytes (e.g., SAR 650984 or daratumumab)
aPTT	activated partial thromboplastin time
ASCT	autologous stem cell transplantation
AST	aspartate transaminase (SGOT)
ATRA	all trans retinoic acid
AUC <sub>last</sub>	area under the curve, first-last measurement
AUC <sub>(0-∞)</sub>	area under the curve, time zero to last
AV	arterioventricular
BCNU	bis-chloroethylnitrosourea
Benda	bendamustine
bid	twice daily
BMSC	bone marrow stroma cells
BP	blood pressure
BSA	body surface area
BSC	best supportive care
BUN	blood urea nitrogen
°C	degrees Centigrade
carf	carfilzomib
CBC	complete blood count
CBR	clinical benefit rate
CD	cluster of differentiation
CD-ROM	compact disc, read-only-memory
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
Cis	cisplatin
CLL	chronic lymphocytic leukemia

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<b>Abbreviation</b>	<b>Definition</b>
Cm	centimeter
C <sub>max</sub>	maximum serum concentration
CML	chronic myeloid leukemia
CNS	central nervous system
CR	complete response
CRA	clinical research associate
CRF	case report form
CRM1	chromosomal region maintenance protein 1
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
cyclo	cyclophosphamide
DCR	disease control rate (CR, Cri, PR, SD $\geq$ 4 weeks)
Dex	dexamethasone
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DOR	duration of response
Dox	doxorubicin
DSMB	Data Safety Monitoring Board
DT	dexamethasone + thalidomide
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
F%	oral bioavailability
°F	degrees Fahrenheit
FACT-G	Functional Assessment of Cancer Therapy (general version)
FACT-MM	Functional Assessment of Cancer Therapy - Multiple Myeloma
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin embedded
FISH	fluorescent in situ hybridization

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<b>Abbreviation</b>	<b>Definition</b>
FLC	free light chain
FLT3	fms-like tyrosine kinase
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GM-CSF	granulocyte macrophage-colony stimulating factor
GRP	growth regulatory protein
GSH	glutathione
Hb	hemoglobin
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPLC/MS-MS	high performance liquid chromatography/tandem mass spectrometry
hr	hour
IC <sub>50</sub>	inhibitory concentration, 50% (half maximal inhibitory concentration)
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN $\alpha$	interferon alpha
IFN $\gamma$	interferon gamma
IgA	immunoglobulin A
IgVH	immunoglobulin heavy chain variable region
IL-1 $\alpha$	interleukin 1 alpha
IL-6	interleukin 6
IL-8	interleukin 8
IL-10	interleukin 10
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
INR	international normalization ratio
IRB	Institutional Review Board

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<b>Abbreviation</b>	<b>Definition</b>
ISS	International Staging System
ITT	intent-to-treat
IV	intravenous
kg	kilogram
KM	Kaplan-Meier
LAFB	left anterior fascicular block
LDH	lactate dehydrogenase
LMW	low molecular weight
LOCSIII	Lens Opacities Classification System
m <sup>2</sup>	square meters
MAb	monoclonal antibody
MCL	mantle cell lymphoma
MCP1	monocyte chemo-attractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	myocardial infarction
min	minute
miRNA	microRNA
mL	milliliter
mITT	modified Intent-to-Treat
MM	multiple myeloma
mmHg	millimeters of mercury
MTD	maximum tolerated dose
MR	minor response
mRNA	messenger ribonucleic acid
MUGA	multiple gated acquisition
5'NT	5'-nucleotidase
NAC	N-acetylcysteine
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NES	nuclear export sequences
NHL	non-Hodgkin's lymphoma
NK1R	neurokinin 1 receptor



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<b>Abbreviation</b>	<b>Definition</b>
NPC	nuclear pore complex
NPM1	nucleophosmin
NYHA	New York Heart Association
OPG	osteoprotegerin
ORR	overall response rate
OS	overall survival
PACE	cisplatin, doxorubicin, cyclophosphamide, and etoposide
PCR	polymerase chain reaction
PD	progressive disease
PDn	pharmacodynamic
PE	physical examination
penta-refractory	refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and anti-CD38 MAb (SAR 650984 or daratumumab)
PFS	progression free survival
PI	proteasome inhibitor (within drug treatment context)
PI	principal investigator (within clinical context)
PK	pharmacokinetic
po	by mouth
PP	per protocol
PPI	proton pump inhibitor
pred	prednisone
PVC/PE/PCTFE	polyvinyl chloride/polyethylene/polychlorotrifluoroethylene
PR	partial response
prn	as needed
PT	prothrombin time
qAM	every morning
qd	once daily
qhs	at bedtime
qid	four times daily
QoL	quality of life
qRT-PCR	quantitative real time polymerase chain reaction
quad-refractory	refractory to bortezomib, carfilzomib, lenalidomide, and pomalidomide
RBBB	right bundle branch block
RBC	Red blood cell

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<b>Abbreviation</b>	<b>Definition</b>
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RPPA	reverse phase protein array
RR	resistant/refractory
RT	Richter's transformation
SAE	serious adverse event
SAM	S-adenosylmethionine
sCR	stringent complete response
SD	stable disease (within clinical context)
SD	standard deviation (within statistical context)
SIADH	Syndrome of Inappropriate Antidiuretic Hormone Secretion
SINE	selective inhibitor of nuclear export
SOC	standard of care (within treatment context)
SOC	system organ class (within adverse event context)
SOP	standard operating procedure
SPEP	serum protein electrophoresis
TD	thalidomide and dexamethasone
TEAE	treatment-emergent adverse event
tid	three times daily
TK	toxicokinetic
T <sub>max</sub>	time to maximum serum concentration
TNF $\alpha$	tumor necrosis factor alpha
TOI	trial outcomes index
TSH	thyroid stimulating hormone
TSP	tumor suppressor protein
TTP	time to progression
TUNEL	terminal deoxyribonucleotidyl transferase-dUTP nick end labeling
ULN	upper limit of normal
UPEP	urine protein electrophoresis
VEGF $\alpha$	vascular endothelial growth factor alpha
vel	Velcade (bortezomib)
vid	vincristine, ifosfamide, and doxorubicin
vinc	vincristine
VRD	Revlimid (lenalidomide), Velcade (bortezomib) and dexamethasone

---

<b>Abbreviation</b>	<b>Definition</b>
VGPR	very good partial response
WBC	white blood cell
XPO1	exportin 1

## 1 OVERVIEW

Multiple myeloma (MM) is the second most common hematological malignancy (after non-Hodgkin's lymphoma), representing 1% of all cancers and 2% of all cancer deaths. Despite the increased effectiveness of first-line agents, the majority of patients will eventually relapse and become resistant to all classes of available anti-MM therapies. With over 15,000 deaths from MM expected in 2014 in the USA alone, there remains a need for novel therapies for the treatment of refractory MM that can improve the overall survival rate.

Selinexor is a Selective Inhibitor of Nuclear Export (SINE) compound that binds and inactivates Exportin 1 (XPO1), thereby forcing the nuclear retention of key tumor suppressor proteins (TSPs). XPO1 protein levels are significantly elevated in MM, leading to the nuclear exclusion of TSPs, the glucocorticoid receptor (GR), and enhanced translation of certain oncogene mRNAs (*Tai et al., 2014*). Transient retention of TSPs in the nucleus at high levels via XPO1 blockade activates their cell cycle checkpoint and genome surveying actions. This leads to the death of nearly all types of malignant cells, whereas normal cells undergo transient cell cycle arrest and recovery when the export block is released. XPO1 also exports the GR, leading to attenuation of its transcriptional activity. In the presence of glucocorticoids, XPO1 blockade leads to nuclear accumulation and activation of the GR. In addition, XPO1 inhibition leads to the nuclear entrapment of cap-binding protein (eIF4E)-dependent oncogene mRNAs, thus preventing their translation into proteins in the cytoplasm. In this way, SINEs lead to reduction in key oncoproteins such as c-Myc, Cyclin D, hDM2 and others. The reactivation of multiple TSP pathways as well as glucocorticoid signaling, along with reduced translation of key oncoproteins through inhibition of a non-redundant, single protein, i.e., XPO1, represents a novel approach to the treatment of neoplastic diseases including those with multiple genomic alterations and resistance mechanisms.

First-in-human Phase 1 studies with oral selinexor are being conducted in advanced hematological malignancies including non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), multiple myeloma (MM), and acute myeloid leukemia (AML) (KCP-330-001), in solid tumors and in soft tissue and bone sarcomas (KCP-330-002 and -003). In addition, Phase 2 studies are underway or are pending initiation in glioblastoma, gynecological malignancies, squamous cell carcinoma, prostate cancer, acute myeloid leukemia (AML), diffuse large B-cell lymphoma (DLBCL), and Richter's transformation. More than 550 patients with objectively progressing tumors at study entry have received selinexor as of December 15, 2014.

The main side effects of selinexor seen in heavily pretreated Phase 1 patients to date are anorexia, fatigue, nausea, diarrhea, and thrombocytopenia. These adverse events (AEs) are mainly Grades 1 and 2, and may be mitigated or eliminated with standard supportive care. In addition, their prevalence and intensity typically decline after 4-8 weeks of treatment. As of December 15, 2014, there are no known cumulative or major organ toxicities associated with selinexor, and several patients with heavily pretreated, resistant/refractory (RR) cancers have received single-agent selinexor for >12 months; the longest treatment duration thus far is > 2 years.

Selinexor has shown single-agent, durable, anti-cancer activity in patients with multiple RR hematologic and solid tumor malignancies, including MM, at doses of  $\geq 6$  mg/m<sup>2</sup> body surface area (BSA) in these initial Phase 1 dose-escalation studies. In addition, results from a small number (10) of patients suggests that selinexor in combination with “low dose” dexamethasone (20 mg) has increased efficacy in RR MM patients relative to selinexor alone.

In the current study, patients will also receive dexamethasone to both improve the tolerability of selinexor and provide additional efficacy benefit as selinexor has been shown to activate glucocorticoid signaling through its receptor. Dexamethasone has been shown in previous studies to be an effective prophylactic treatment for the common AEs of selinexor described above. While untreated MM is exquisitely sensitive to glucocorticoids, this benefit wanes over time with treatment, which usually includes glucocorticoids in combination therapy. Multiply relapsed MM is unlikely to respond to glucocorticoid treatment alone, but dexamethasone should provide symptomatic relief of selinexor-associated toxicity, and may provide synergistic efficacy in combination with selinexor, which can reactivate GR signaling. The current study will evaluate selinexor combined with low-dose dexamethasone for the treatment of MM in patients whose disease is quad-refractory (i.e., refractory to bortezomib, lenalidomide, carfilzomib, and pomalidomide).

## 2 MULTIPLE MYELOMA (MM)

MM is a hematological malignancy characterized by the accumulation of monoclonal plasma cells in the bone marrow, the presence of monoclonal immunoglobulin, or M protein in the serum or urine, bone disease, kidney disease, and immunodeficiency. It is more common in elderly patients (median age at diagnosis is 65–70 years; only 2% of patients are younger than 40 years) (*Raab 2009*).

MM is the second most common hematological malignancy (after non-Hodgkin’s lymphoma), representing 1% of all cancers and 2% of all cancer deaths. With current therapy, median survival is 5.2 years after diagnosis (*Kumar 2014*).

Although the cause of MM is unknown, a number of mutated genes have been found with significant frequency in patients with MM. These include mutations in NRAS, KRAS, TP53 and BRAF, which are well known oncogenic drivers for other cancers (*Lohr 2014*) and mutations in many genes associated with NF $\kappa$ B activation (*Keats 2007*). Also, certain risk factors make patients more susceptible to the disease. MM is more common in individuals over the age of 65, in males, and in those with family members affected by MM. Fifty percent (50%) of patients with MM harbor mutations in the immunoglobulin heavy-chain locus on chromosome 14q32, partial or complete loss of chromosome 13, and partial loss of chromosome 17 (*Raab 2009; Kyle 2004*).

The diagnosis of MM is based on the key characteristics of the disease, occupation of the bone marrow cavity, the presence of space occupying bone lesions, and the production of paraprotein (*Raab 2009; International Myeloma Working Group 2003*). The staging of MM is based on  $\beta_2$ -microglobulin level, which is directly correlated to renal function, tumor mass, and albumin level (*Greipp 2005*). The stages are described in *Appendix 2*.

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The treatment of MM has improved in the last 20 years due to the use of high-dose chemotherapy (i.e., alkylating agents) and autologous stem cell transplantation, the introduction of immunomodulatory agents, such as thalidomide, lenalidomide, and pomalidomide, and the proteasome inhibitors, bortezomib and carfilzomib. However, despite the increased effectiveness of these agents, most patients develop highly resistant MM and succumb to the disease. With over 15,000 deaths from MM expected in the USA in 2014, there remains a high unmet medical need to develop anti-MM agents with novel mechanisms.

### 3 NUCLEAR EXPORT

#### 3.1 INHIBITION OF XPO1 IN HUMAN CANCER

Many important tumor suppressing proteins (TSPs) have been identified in cancer pathogenesis, including but not limited to TP53, FOXO3a, I $\kappa$ B, BRCA1, APC, PP2A, and Rb (Turner 2012; Senapedis 2014; Tan 2014; Yang 2014). TSPs mediate tumor suppression pathways via various functions including recognition of cellular damage, arrest of the cell cycle until repairs can be made, and induction of apoptosis in cells that are beyond repair (Brown 2011). Similarly, glucocorticoid binding to, and nuclear localization of, the glucocorticoid receptor (GR) is required for its signaling.

The tumor suppression and anti-cancer activity of these TSPs and the GR requires their presence in the nucleus. Conversely, export to the cytoplasm by nuclear export shuttle protein XPO1 can inactivate their abilities to regulate cellular processes (Xu 2010) and cancer cells exploit these functions to successfully evade normal DNA-damage controls as well as anti-neoplastic therapy. XPO1 is the only known nuclear export protein for the vast majority of TSPs and the GR. Of note, XPO1 has been identified as a selective survival gene in MM by unbiased high-throughput short interfering ribonucleic acid (siRNA) screening (Tiedemann 2012) and is commonly overexpressed in MM (Tai 2014).

XPO1 blockade causes transient nuclear retention of TSPs, the GR, and other growth modulators, re-establishing their tumor suppressing and growth regulating effects on cancer cells and potentially reversing mechanisms leading to chemotherapy resistance (which holds possible future implications for combination therapies) (Lain 1999).

Certain growth-promoting (including oncogene) messenger RNAs (mRNAs) require specialized nuclear export via a “cap-binding complex” in order to exit the nucleus into the cytoplasm where they are translated into proteins (Culjkovic 2013; Koehler 2007). Several key MM genes including c-Myc, Cyclin D1, hDM2 and others utilize this complex via binding to the protein eIF4E in order to exit the nucleus and undergo efficient translation into protein. The cap-binding complex protein eIF4E is exported out of the nucleus into the cytoplasm exclusively by XPO1. As these proteins tend to have very short half-lives, constant translation is required to maintain their cellular levels. Inhibition of XPO1-mediated nuclear export leads to reduced translation of these growth-promoting proteins, and subsequently significant drops in their levels.

In normal cells, XPO1 inhibition transiently arrests the cell cycle without cytotoxicity followed by recovery after the inhibitor is removed (Lain 1999; van der Watt 2009; Gray 2007). Several attempts to develop this class of anti-cancer drug have failed due to off-target effects of the drugs which led to significant weight loss, diarrhea, and marked fatigue and asthenia in the early clinical trials (Mutka 2009; Newlands 1996; Roberts 1986).

It is now well recognized that forced nuclear retention of TSPs can counteract a multitude of oncogenic, growth stimulatory (and inflammatory) pathways that perpetuate the neoplastic phenotype. Similarly, nuclear retention of the GR in the presence of glucocorticoids could restore its activity. Finally, inhibition of eIF4E/XPO1-mediated mRNA export of oncoproteins lead to reductions in their levels. Because restoration of TSP  $\pm$  GR activity and reduction in

oncogenic signals are relevant to essentially any cancer, XPO1 inhibition is expected to have activity against MM and many other malignancies (*Table 3.1*).

**Table 3.1 Effect of XPO1 Inhibition on Oncogenic and Inflammatory Pathways**

Pathway Affected	Effect of XPO1 Inhibition	Reference
XPO1 overexpression	XPO1 reduction	Walker 2013
Glucocorticoid Receptor (GR) Inactivation (nuclear export)	Nuclear GR retention (in presence of glucocorticoids) and reactivation	Chen 2014
p53 mutation	p73 activation, p21 activation	Ranganathan 2012
hDM2 (MDM2) activation	Nuclear p53 retention and activation, hDM2 protein reduction	Kojima 2013
c-Myc amplification	MYC protein reduction	Schmidt 2013
Cyclin D1 overexpression	Cyclin D1 reduction	Gao 2014
NPM1 mutation	Restoration of nuclear NPM1	Falini 2007
CEBPA down-regulation	Nuclear retention and activation	Ranganathan 2012
CDKN2A reduction	p53/p73 stabilization	Azmi 2013
Rb reduction	Rb hypophosphorylation, p14/p16 elevation	Fragomeni 2013
FLT3 activation	FLT3 reduction	Ranganathan 2012
c-KIT activation	c-KIT reduction	Ranganathan 2012
NF-κB activation	IκB nuclear retention and activation	Lapalombella 2012
PIK3 or AKT activation	FOXO1, -3, -4 activation	Lapalombella 2012
Survivin – cytoplasmic	Survivin nuclear retention	Altura 2003
Bcr-Abl activation	PP2A activation	Walker 2013



## 4 SELINEXOR (KPT-330)

### 4.1 INTRODUCTION

SINE compounds, a new generation of XPO1 inhibitors, were designed as drug-like small molecules that selectively inhibit XPO1 in order to increase efficacy and reduce toxicity secondary to non-specific binding and off-target effects.

Mechanistic studies show that SINE compounds induce nuclear localization and activation of multiple TSPs, along with reduction in oncoprotein levels (e.g., c-Myc and the anti-apoptotic protein BCL-X<sub>L</sub>) leading to rapid apoptosis of MM cells (*Tai 2014*).

Selinexor is an oral, first in class, slowly reversible, potent SINE compound that specifically blocks XPO1. Selinexor restores many of the TSPs to the nucleus where they can carry out their normal functions. It is selectively cytotoxic for cells with genomic damage (i.e., tumor cells), both *in vitro* and *in vivo*. All cell types exposed to SINE compounds *in vitro* undergo G1 ± G2 cell cycle arrest, followed by a ‘genomic fidelity’ review. Cells with damaged genomes are induced to undergo apoptosis. Normal cells, with an intact genome, remain in transient, reversible cell cycle arrest until the export block is relieved. Selinexor and other SINE compounds are not intrinsically cytotoxic; rather, they can restore the highly effective TSP pathways that lead to selective elimination of genomically damaged (i.e., neoplastic) cells. SINE compounds also lead to restoration of glucocorticoid receptor (GR) signaling in the presence of glucocorticoids, and reduction in oncoprotein levels (e.g., c-Myc, Cyclin D1, hDM2, Bcl-X<sub>L</sub> and others). Tumors of hematopoietic lineage are particularly susceptible to induction of apoptosis by XPO1 inhibition; normal hematopoietic cells and their functions are largely spared.

### 4.2 PRECLINICAL DATA

In this section, a brief summary of preclinical data is provided. More detailed information is presented in the current *Selinexor/KPT-330 Investigator’s Brochure*.

#### 4.2.1 Pharmacology Studies

*In vitro* experiments with continuous (~72 hour) exposure to selinexor demonstrated potent pro-apoptotic activity across a broad panel of tumor-derived cell lines and patient samples in culture, including multidrug-resistant cancers. Moreover, selinexor demonstrated cytotoxicity in MM and CLL cells in the absence or presence of bone marrow stroma cells (BMSC).

Pharmacokinetic studies were conducted in mice, rats and monkeys. Selinexor showed dose proportional exposure with no accumulation. Please see the current *Selinexor/KPT-330 Investigator’s Brochure* for more information.

Several studies were conducted to evaluate the effect of SINE compounds on MM *in vivo*. In MM1.S xenograft tumors, treatment with the SINE compound KPT-276 showed a marked decreased in tumor volume (40%) whereas tumor volume increased by 36% with placebo (*Schmidt 2013*). KPT-276 was also active in the Vk\*MYC mouse model of MM, which has a positive predictive value of 67% for the activity of single-agent compounds in clinical trials (*Schmidt 2013; Chesi 2012*).

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#### 4.2.1.1 Selinexor plus Dexamethasone Combination Studies

Selinexor and dexamethasone in combination were found to have a synergistic effect on reducing MM1.S human MM cell viability relative to either drug alone (*Chen 2014*). Increased glucocorticoid receptor (GR) nuclear localization and concomitantly activated GR-mediated transcription in the presence of glucocorticoids were at least partly responsible for the synergistic cytotoxicity of the selinexor/dexamethasone combination in MM1.S cells (*Gao 2014*).

Enhanced activity of the selinexor/dexamethasone combination was also observed in two xenograft models of human MM. The addition of dexamethasone to selinexor enhanced activity (86%) relative to selinexor alone.

In summary, the combination of selinexor and dexamethasone is synergistic *in vitro* and *in vivo* in MM cell cytotoxicity assays through increased nuclear localization of GR and amplified GR transcriptional activity. Selinexor has also shown additive or synergistic activity when combined with other MM drugs including proteasome inhibitors (*Turner 2013; Turner 2014; Tai 2014*), topoisomerase II inhibitors (*Turner 2013*), and lenalidomide (*data on file*). Taken together, these studies demonstrate that SINE compounds are active anti-MM compounds that cause decreased cell viability, increased apoptosis, and cell cycle arrest *in vitro* and potent inhibition of MM tumor growth *in vivo*, and that the addition of dexamethasone can augment these effects.

### 4.3 CLINICAL EXPERIENCE

As part of the Phase 1 clinical trial of selinexor in patients with advanced hematological malignancies (KCP-330-001), patients with multiple myeloma were treated with either single-agent selinexor or selinexor in combination with low-dose (20 mg) dexamethasone, both dosed twice weekly. Forty-four patients with MM whose disease was relapsed and/or refractory to all available classes of approved therapies with a mean of 5.7 prior therapies and progressing on study entry have been enrolled in this trial as of 07 July 2014. Of these 44 patients, 34 received single-agent selinexor therapy and ten patients were treated with selinexor in combination with low-dose dexamethasone.

Among 29 patients receiving single-agent selinexor therapy, best responses include 1 PR (3%), 6 MRs (21%), 16 SDs (55%), and 6 PDs (21%) (see *Table 4.1*). It should also be noted that some patients treated with single-agent selinexor also received very low doses of dexamethasone (12 mg with each dose of selinexor) or another glucocorticoid as part of supportive care.

In this study, ten patients were treated with 45 mg/m<sup>2</sup> BSA (~80 mg) of selinexor and 20 mg of dexamethasone, both dosed twice weekly. This dose of dexamethasone is the standard low dose dexamethasone (40 mg weekly or 20 mg twice weekly) used with other anti-myeloma drugs, including lenalidomide or pomalidomide. The patients enrolled in this study had received a median of 6.5 prior courses of therapy. All had received prior therapy with at least one proteasome inhibitor (e.g., carfilzomib and/or bortezomib), at least one IMiD (e.g., lenalidomide and/or pomalidomide), and glucocorticoids (typically two or more times), while nine of the ten patients also received stem cell transplantations including high-dose alkylating agents (*Table 4.2*).

As of 15 Dec 2014, the best responses (*Table 4.1*) among nine patients who received selinexor plus dexamethasone were one stringent complete response (sCR) (11%), 5 PRs (55%), 2 MRs (22%), and 1 PD (11%). One patient was non-evaluable. The CBR was 89% and the ORR was 67%. Eleven additional patients with MM were dosed with selinexor 60 mg/m<sup>2</sup> (~100 mg) in combination with 20 mg dexamethasone in this ongoing study, but this dose was found to be poorly tolerated due to high levels of Grade 3 fatigue, nausea and vomiting (*Chen, 2014*). In this heavily pre-treated Phase 1 population, several patients have remained on this combination for > 6 months (*Table 4.2*).

**Table 4.1 Responses in Evaluable MM Patients - Study KCP-330-001 (01 Dec 2014)**

Treatment	N	CBR	ORR	sCR	PR	MR	SD	PD
Selinexor Low ≤ 30mg/m <sup>2</sup>	15	4 (27%)	-	-	-	4 (27%)	8 (53%)	3 (20%)
Selinexor High ≥ 35mg/m <sup>2</sup>	14	3 (21%)	1 (7%)	-	1 (7%)	2 (14%)	8 (57%)	3 (21%)
Total Selinexor (Low + High)	29	7 (24%)	1 (3%)	-	1 (3%)	6 (21%)	16 (55%)	6 (21%)
Selinexor (45 mg/m <sup>2</sup> ) + Dex (20 mg)*	9	8 (89%)	6 (67%)	1 (11%)	5 (55%)	2 (22%)	-	1 (11%)

\*One patient was not evaluable.

Abbreviations: N = number of patients; Dex = dexamethasone; CBR = clinical benefit response (MR+PR+sCR); ORR = overall response rate (PR+sCR); sCR = stringent complete response; PR = partial response; MR = minor response; SD = stable disease; PD = progressive disease; NE = non-evaluable.

Source: Chen 2014

**Table 2.2 MM Treatment History and Time on Treatment - Study KCP-330-001 (01 Dec 2014)**

Patient ID	MM Type	Max. % Change	Response	# Prior Therapies	Prior Therapies	Study Days
76	IgG-κ	- 71%	PR	7	Dox-Vinc-Dex, TD-Dex, Carfil-Dex, VRD, Cyclo-Pred-BCNU, Dox-Carf-Dex	301+
77	FLC-λ	-	NE	8	Len-Dex, Cyclo-Etop-Cis-Mel-Dex-ASCT, VRD, Carf-Cyclo-Dex, Carf-Cyclo-Dex-Len, Carm-TDC, Cis-Etop-Cyta-Vel-Mel, Cyclo-Carf-Pom-Dex, Vor-Len-Dex	15
79	FLC-κ	-53%	PR	3	TD-Pred-Dex-ASCT, Cyclo-Vel-Dex, Len-Dex	52
81	FLC-κ	-99%	sCR	5	Vinc-Adria-Dex-ASCT, ASCT-Len-Dex, Cyclo-Pred, Pom-Carf-Dex	280
84	IgG-κ	-84%	PR	9	Vel-Dex, ASCT, Len-Dex, Vel-Dex, Vel, Carfil, Pom-Dex, Carf, DT-PACE-TD	170
90	IgG-κ	41%	PD	5	Cyclo-Vel-Len-Dex (x2), Carf-Mel-ASCT, Cyclo-Vel-Dex, Pom-Carf-Dex	31
92	IgA-κ	-55%	PR	10	Vel-Dex, VRD-ASCT, Len, Reolysin, TG02, Carfil-Dex, Carfil-Cyclo-Dex, Carfil-Pom-Dex	121
93	IgG-κ	-41%	MR	9	VAD, VTD+ASCT, Vel-Len-Dex, Experim, Carfil-Panob, Len-Elotu-Dex, Experim, Pom-Dex, Benda-Pom-Dex	114
98	IgG-λ	-48%	MR	16	Len-Dex, ASCT (x2), Vel-Len-Dex, Vid-Len, Benda-Vel-Dex, VAD, Ritux, Vel-TD, Carfil-Dex, Carfil-Dex-Cis-Adria, Len-Ritux-Inter, Carfil-Pom, Vel-TD-Dex-Adria-ATRA-Arsenic Trioxide, Len-Dex, TG02-Carf	79
99	IgA-κ	-82%	PR	6	Sal, TD-Dex, Len, ASCT, Ibrut, Vel-Dex	201+

+ Patient still on study as of 15 Dec 2014.

Abbreviations: ID = identification number; MM = multiple myeloma; # = number; FLC = free light chain; Ig = immunoglobulin; sCR = stringent complete response; PR = partial response; MR = minor response; PD = progressive disease; NE = non-evaluable; Dex = dexamethasone; Dox = doxorubicin; Vinc = vincristine; TD = thalidomide and dexamethasone; carfil = carfilzomib; Cyclo = cyclophosphamide; Pred = prednisone; BCNU = bis-chloroethylnitrosourea; Len = lenalidomide; Carm = carmustine; Etop = etoposide; Cis = cisplatin; Adria = adriamycin; ASCT = autologous stem cell transplantation; ATRA = all trans retinoic acid; VRD = Revlimid (lenalidomide), Velcade (bortezomib) and dexamethasone; DT = thalidomide and dexamethasone; PACE = cisplatin, doxorubicin, cyclophosphamide, and etoposide.

Source: Chen 2014

Adverse events in patients receiving single-agent selinexor were generally low-grade, consistent with events observed in patients with other hematological malignancies and responsive to standard supportive care. Compared with selinexor given alone, fewer AEs were

reported in patients receiving selinexor plus dexamethasone, particularly levels of nausea, consistent with dexamethasone's reduction in selinexor related side effects of nausea, anorexia, and fatigue.

In addition to patients with MM achieving durable responses and disease control on selinexor single-agent therapy, selinexor with low-dose dexamethasone showed activity with rapid M-protein reductions and good tolerability, even in patients with disease refractory to pomalidomide.

Bone marrow biopsies from a total of nine MM patients were obtained prior and 3-4 weeks post-selinexor treatment initiation. An overall reduction in malignancy was observed in all patients. Specifically, histology showed that post-treatment marrows had noticeably fewer myeloma cells and increased areas of adipocytes and dense hematopoiesis, typical of normal marrow. Increases in nuclear staining provide evidence of the tumors' direct response to selinexor.

#### **4.3.1 Potential Risks**

Selinexor is currently in clinical development and has not been approved by the FDA for commercial use. Human experience with selinexor has been evaluated in > 550 patients (as of 15 Dec 2014) and the entire safety profile is not known at this time. Measures will be taken to ensure the safety of the patients participating in this trial, including the use of stringent inclusion and exclusion criteria and close monitoring.

If toxicities are encountered, adjustments will be made to the study treatment as detailed in the sections below. All AEs and serious adverse events (SAEs) will be recorded during the trial and for up to 30 days after the last dose of study treatment or until the initiation of another anti-cancer therapy, whichever occurs first.

In the ongoing clinical study, the most common AEs suspected to be related to selinexor are anorexia, fatigue, nausea, vomiting, diarrhea, and thrombocytopenia. Virtually all of these side effects can be managed effectively with dose modification and/or supportive care initiated prior to first dosing. Overall, the most frequently observed laboratory abnormalities include thrombocytopenia, hyponatremia, and a decrease in red blood cells. The majority of these have been mild to moderate. Please refer to the current *Selinexor/KPT-330 Investigator's Brochure* for the most current information.

One patient, heavily pre-treated for recurrent pancreatic cancer, developed acute cerebellar syndrome following 4 doses of selinexor at 85 mg/m<sup>2</sup> BSA twice weekly. The patient experienced abnormal speech, loss of coordination, and was unable to walk. Since the time of the initial reported event, this patient is recovering and both her speech and mobility have recovered to near baseline over ~6 weeks. No other patients have reported such symptoms to date.

#### **Reproductive Risks**

Patients should not become pregnant or father a child while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important that patients understand the need to use birth control while on this study. Female

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patients of child bearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at screening, and male patients must use an effective barrier method of contraception if sexually active with a female of child bearing potential. Acceptable methods of contraception are condoms with contraceptive foam; oral, implantable or injectable contraceptives; contraceptive patch; intrauterine device; diaphragm with spermicidal gel; or a sexual partner who is surgically sterilized or post-menopausal. Total (true) abstinence (when this is in line with the preferred and usual lifestyle of the patient), is an acceptable method of contraception. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose.

## 5 RATIONALE FOR THE STUDY

Multiple myeloma is the second most common hematological malignancy. With conventional treatment methods, median survival is 5.2 years after diagnosis (*Kumar 2014*). Multiple myeloma is highly treatable but is not considered to be curable with currently available therapies. Common treatments include glucocorticoids, chemotherapy, proteasome inhibitors, immunomodulatory drugs, stem cell transplants, and radiation therapy.

Selinexor has demonstrated anti-MM activity in pre-clinical studies *in vitro* and *in vivo*. In the initial clinical study of selinexor in MM, 44 patients with MM whose disease was relapsed and/or refractory to all available classes of approved therapies, with a mean of 6.5 prior therapies and progressing on study entry, have been enrolled as of 15 Dec 2014. Of these 44 patients, 34 received single-agent selinexor therapy and ten patients were treated with selinexor in combination with dexamethasone. Preliminary evidence of efficacy was seen in both the single-agent and the low-dose dexamethasone combination groups (see *Table 4.1* and *Table 4.2*).

Based on the demonstrated activity of selinexor in heavily pretreated patients with RR MM, the current study is designed to confirm the activity of selinexor plus low-dose dexamethasone in approximately 80 patients with heavily pretreated MM that is quad-refractory to bortezomib, carfilzomib, lenalidomide, and pomalidomide. In addition, approximately 25% of enrolled patients must be penta-refractory (i.e., quad-refractory *plus* refractory to anti-CD38 MAb [e.g., SAR 650984 or daratumumab]).

This is a Phase 2b, single-arm, open-label, multicenter study of selinexor (80 mg) with low-dose (20 mg) dexamethasone given orally. This trial is designed with ORR and DOR as endpoints for the entire study population. In addition, the safety of selinexor at doses up to 100 mg (an escalation option under certain conditions) when combined with concomitant dexamethasone treatment will, be assessed.

### 5.1 RATIONALE FOR SELINEXOR DOSE SCHEDULE

More than 550 patients with advanced cancers have received selinexor orally in Phase 1 and Phase 2 studies of selinexor, as of 15 Dec 2014. In a Phase 1 dose-escalation study in patients with advanced hematologic malignancies that began enrollment in July 2012, the maximum tolerated dose (MTD) has not been reached on a twice-weekly dosing schedule up to selinexor doses of 60 mg/m<sup>2</sup> BSA. Furthermore, a dose of 70 mg/m<sup>2</sup> twice weekly has cleared dose limiting toxicity (DLT) evaluation in patients with heavily pretreated AML. However, a MTD of 65 mg/m<sup>2</sup> twice weekly has been determined in another ongoing Phase 1 study of selinexor in patients with advanced solid tumors. As described earlier, two DLTs occurred in 2 patients in this solid tumor study treated at 85 mg/m<sup>2</sup> twice weekly and included ‘probably related’ asymptomatic Grade 3 hyponatremia and ‘possibly related’ acute cerebellar syndrome with ataxia and dysarthria (which reverted to approximately baseline over two months). Dosing above 70 mg/m<sup>2</sup> twice weekly has therefore been discontinued in all studies at this time and will serve as the maximum allowable dose.

Patients in the present study will receive selinexor 80 mg (45 mg/m<sup>2</sup> BSA) plus low-dose dexamethasone (20 mg), both twice weekly.

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In select cases (e.g., for patients showing SD or PR and tolerating treatment particularly well), the selinexor dose may be increased by 20 mg. The dose level for an individual patient may be escalated based on efficacy and safety considerations after a minimum of 2 cycles of study therapy. However, as described above, in no case may the dose for any patient exceed 70 mg/m<sup>2</sup>. Prior to any potential dose increase, the BSA for the patient will be calculated. Patients with BSA < 1.4 m<sup>2</sup> may not have their dose increased, as this would result in a dose > 70 mg/m<sup>2</sup> selinexor.



## 6 STUDY OBJECTIVES

### 6.1 PRIMARY OBJECTIVES

- Determine the Overall Response Rate (ORR), including Partial Response (PR), Very Good Partial Response (VGPR), Complete Response (CR), and stringent complete response (sCR) to selinexor 80 mg plus low dose dexamethasone (20 mg) in patients with MM quad-refractory to prior treatment with bortezomib, carfilzomib, lenalidomide, and pomalidomide.
- Evaluate the efficacy of selinexor plus dexamethasone in comparison to a minimally effective lower threshold level of ORR (i.e., 15%).

### 6.2 SECONDARY OBJECTIVES

- Determine Duration of Response (DOR = the length of time from when measurement criteria for response were first met until the date of first recurrence, progressive disease [PD] or death)
- Determine the Clinical Benefit Rate (CBR = sCR + CR + PR + Minor Response [MR]), and duration of CBR
- Determine the Disease Control Rate (DCR = CBR + stable disease [SD; for a minimum of 12 weeks]), as well as duration of DCR
- Determine Progression Free Survival (PFS = length of time from first dose of study drug to objective evidence of confirmed disease progression)
- Compare Time to Progression (TTP) obtained with study treatment versus the patient's TTP(s) on prior therapies for MM
- Determine the Overall Survival (OS) of patients with quad-refractory MM treated with selinexor + dexamethasone.
- Compare PFS, ORR, DOR, DCR, and OS obtained with selinexor + dexamethasone in patients with International Staging System (ISS) Stage III versus ISS Stages I or II
- Assess ORR, DOR, CBR, OS, disease control and PFS in the sub-group of patients (25%) with penta-refractory MM (i.e., refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide and an anti-CD38 MAb [e.g., SAR 650984 or daratumumab])
- Assess Quality of Life (QoL) using the Functional Assessment of Cancer Therapy - Multiple Myeloma (FACT-MM)
- Describe pharmacokinetic (PK) properties of selinexor in patients with quad-refractory MM
- Evaluate pharmacodynamic (PDn) changes in selected markers following treatment
- Assess safety by frequency and severity of AEs and changes in physical examinations, vital signs and laboratory values from baseline

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### 6.3 EXPLORATORY OBJECTIVES

- Compare ORR, DOR, PFS, and OS in patients with free light chain (FLC) MM treated with selinexor plus dexamethasone
- Assess ORR, DOR, PFS, and OS in patients receiving dose increases during the study
- Correlational studies to evaluate response as related to:
  - Cytogenetic and fluorescence *in situ* hybridization (FISH) prognostic markers including p53 abnormalities and chromosomal aberrations (e.g., del 17p, t(4;14), t(14;16), del 13) and other MM cytogenetic classifications
  - Gene expression and plasma protein levels
  - Time since initial diagnosis of active myeloma
  - Lytic lesions as measured by skeletal survey

## 7 STUDY DESIGN

### 7.1 OVERVIEW

This is a Phase 2b, single-arm, open-label, multicenter study of selinexor (80 mg) with low-dose (20 mg) dexamethasone given orally to patients with heavily pretreated, quad-refractory MM (refractory to bortezomib, lenalidomide, carfilzomib, and pomalidomide) *and* refractory to their most recent therapy.

A sample size of approximately 80 patients who meet all eligibility criteria and no exclusion criteria will be enrolled to receive study treatment. (Up to 10% additional patients may be enrolled to account for potential drop-outs.) Patients may continue to receive treatment until either disease progression or intolerance has occurred.

Selinexor will be given at an oral fixed dose of 80 mg twice weekly for 3 weeks of each 4-week cycle (6 selinexor doses per cycle); selinexor will not be taken during Week 4.

Dexamethasone (20 mg) will be given with each dose of selinexor *and* during Week 4 of every cycle at the same dose schedule used in Weeks 1-3 (8 dexamethasone doses per cycle). For patients with partial intolerance to glucocorticoids (as determined by the Investigator) a minimum dose of 10 mg dexamethasone with each dose of selinexor is permitted.

In select cases (e.g., for patients showing SD or PR and tolerating treatment particularly well), the selinexor dose may be increased by 20 mg after consultation with the medical monitor. The dose level for an individual patient may be escalated based on efficacy considerations only after a minimum of 2 cycles of study therapy. However, in no case may the dose for any patient exceed 70 mg/m<sup>2</sup>. Prior to any potential dose increase, the body surface area (BSA) for the patient will be calculated and an individual patient's dose may not be increased if it would result in a dose > 70 mg/m<sup>2</sup>.

Patients will also receive best supportive care (BSC) to mitigate selinexor side effects, including blood product transfusions, antimicrobials, and (as appropriate) growth factors including granulocyte colony-stimulating factors for neutropenia, erythropoietins for anemia, and/or platelet-stimulating factors for thrombocytopenia.

The Investigator may remove a patient from study treatment using criteria described in *Section 11*. Patients may decide to discontinue study treatment for any reason. Patients who elect to discontinue study treatment should be encouraged to continue in the study so that follow-up information on disease progression, other antineoplastic therapy, symptoms and survival status may be obtained. However, patients may elect to withdraw consent and decline further participation in the trial at any time.

The Investigator must determine the primary reason for a patient's discontinuation of study treatment and record this information on the electronic case report form (eCRF). Patients who are prematurely withdrawn from study treatment are not eligible to re-initiate study treatment on this protocol at a later date.

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## 7.2 DATA SAFETY MONITORING BOARD

An independent Data Safety Monitoring Board (DSMB) will review the safety of study treatment and any SAEs that occur during the study. The DSMB will develop and follow a data and safety monitoring charter.

The DSMB will include a minimum of two oncologists (at least one of whom specializes in hematologic oncology) and a statistician. The DSMB will be provided with all AE and SAE reports regardless of investigator causality assessments. Following the initial meeting, DSMB meetings will meet on a periodic basis in accordance with the DSMB charter. The chairperson of the DSMB will also be immediately provided with the report of any SAE that is judged as related or possibly related to treatment with study drug.

The charter of the DSMB will specify that this committee is charged with providing periodic reports to Karyopharm that contain recommendations that include, but are not limited to, (a) continuation of the study, and (b) continuation with modification, and (c) termination of the study.

The sponsor will inform IRBs and other relevant parties (e.g., investigators) of any and all DSMB recommended changes to the study and the sponsor's response to those recommended changes.

## 7.3 STOPPING RULES

The entire study or treatment of individual patients may be stopped under defined circumstances as outlined in *Section 11*.

## 7.4 STUDY ENDPOINTS

### 7.4.1 Primary Endpoints

The data used for the primary statistical analysis will be from site data entered in the case report forms (CRFs) (no central laboratories or radiological assessments). Key parameters will be M protein, free light chain, quantitative IgA (for IgA MM patients) and skeletal survey results. The primary endpoints are:

- ORR (sum of PR, VGPR, CR, and sCR) in patients with MM quad-refractory to bortezomib, carfilzomib, lenalidomide, and pomalidomide.
- Efficacy of study treatment in comparison to a minimally effective lower threshold level of ORR (i.e., 15%).

### 7.4.2 Secondary Endpoints

Secondary efficacy variables for study treatment include:

- Determine Duration of Response (DOR = the length of time from when measurement criteria for response were first met until the date of first recurrence, progressive disease [PD] or death)

- Determine the Clinical Benefit Rate (CBR = sCR + CR + PR + Minor Response [MR]), and duration of CBR
- Determine the Disease Control Rate (DCR = CBR + stable disease [SD; for a minimum of 12 weeks]), as well as duration of DCR
- Determine Progression Free Survival (PFS = length of time from first dose of study drug to objective evidence of confirmed disease progression)
- Compare time to progression (TTP) obtained with study treatment versus the patient's TTP(s) on prior therapies for MM
- Determine the Overall Survival (OS) of patients treated with selinexor + dexamethasone
- Compare PFS, ORR, DOR, DCR, and OS obtained with selinexor + dexamethasone in patients with International Staging System (ISS) Stage III versus ISS Stages I or II
- Assess ORR, DOR, CBR, disease control and PFS in the sub-group of patients (25%) with penta-refractory MM (i.e., refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide and an anti-CD38 MAb [e.g., SAR 650984 or daratumumab])
- Assess QoL using the FACT-MM
- Describe PK properties of selinexor in patients with quad-refractory MM
- Evaluate PDn changes in selected markers post treatment
- Assess safety by frequency and severity of AEs and changes in vital signs, physical exams and laboratory findings

#### **7.4.3 Exploratory Endpoints**

- ORR, DOR, PFS, and OS in patient with free light chain (FLC) MM
- ORR, DOR, PFS, and OS in patients undergoing dose increases during the study
- Correlational studies to evaluate response as related to:
  - Cytogenetic and fluorescent *in situ* hybridization (FISH) prognostic markers including p53 abnormalities and chromosomal aberrations (e.g., del 17p, t(4;14), t(14;16), del 13), and other MM cytogenetic classifications, as well as changes in gene and protein expression levels after treatment.
  - Time since initial diagnosis of active myeloma.
  - Lytic lesions as measured by skeletal survey.

#### **7.5 BLINDING AND RANDOMIZATION**

Not applicable; this is an open-label, single-arm, multicenter study.

## 8 SELECTION OF PATIENTS

### 8.1 NUMBER OF PATIENTS

Approximately 80 patients with heavily pretreated, quad-refractory MM who meet all eligibility criteria and no exclusion criteria will be enrolled.

### 8.2 RECRUITMENT

This study will be conducted at multiple sites in the United States.

### 8.3 INCLUSION CRITERIA

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

1. Written informed consent in accordance with federal, local, and institutional guidelines.
2. Age  $\geq 18$  years.
3. Histologically confirmed diagnosis, measurable disease and evidence of disease progression of MM, as described below.
4. Symptomatic MM, based on IMWG guidelines. Patients must have measurable disease as defined by at least one of the following:
  - a. Serum M-protein  $\geq 0.5$  g/dL by serum electrophoresis (SPEP) or for IgA myeloma, by quantitative IgA; or
  - b. Urinary M-protein excretion at least 200 mg/24 hours; or
  - c. Serum Free Light Chain (FLC) whereby the involved light chain measures  $\geq 10$  mg/dL and with an abnormal light chain ratio.
5. Patients must have received  $\geq 3$  prior anti-MM regimens including the following: an alkylating agent, lenalidomide, pomalidomide, bortezomib, carfilzomib and a glucocorticoid. There is no upper limit on the number of prior therapies provided that all other inclusion/exclusion criteria are met.
6. Quad-refractory MM: MM refractory to lenalidomide, pomalidomide, bortezomib, and carfilzomib. Refractory is defined as  $\leq 25\%$  response to therapy, or progression during therapy or progression within 60 days after completion of therapy.
7. Penta-refractory MM: 25% of patients must have MM refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, *and* at least one anti-CD38 MAb (e.g., SAR 650984 or daratumumab)
8. Multiple myeloma refractory to the patient's most recent anti-MM regimen.
9. Eastern Cooperative Oncology Group (ECOG) Performance Status of  $\leq 2$  (*Appendix 1*).
10. Adequate hepatic function within 14 days prior to Cycle 1 Day 1: total bilirubin  $< 2\times$  upper limit of normal (ULN) (except patients with Gilbert's syndrome who must have a total bilirubin of  $< 3\times$  ULN), AST  $< 2.5\times$  ULN and ALT  $< 2.5\times$  ULN.
11. Adequate renal function within 14 days prior to Cycle 1 Day 1: estimated creatinine clearance of  $\geq 20$  mL/min, calculated using the formula of Cockcroft and Gault:

$(140 - \text{Age}) \cdot \text{Mass (kg)} / (72 \cdot \text{creatinine mg/dL})$

Multiply times 0.85 if the patient is female, or CrCl >20 mL/min as measured by 24-hour urine collection.

12. Female patients of child-bearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at screening. Male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized or post-menopausal. Total (true) abstinence (when this is in line with the preferred and usual lifestyle of the patient), is an acceptable method of contraception. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post- ovulation methods) and withdrawal are not acceptable methods of contraception. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose.
13. Adequate hematopoietic function within 14 days prior to Cycle 1 Day 1: total WBC count  $\geq 1,500/\text{mm}^3$ , ANC  $\geq 1000/\text{mm}^3$ , hemoglobin (Hb)  $\geq 8.0 \text{ gm/dL}$ , and platelet count  $\geq 75,000/\text{mm}^3$  (patients in whom <50% of bone marrow nucleated cells are plasma cells) or  $\geq 30,000/\text{mm}^3$  (patients in whom >50% of bone marrow nucleated cells are plasma cells. Patients receiving hematopoietic growth factor support, including erythropoietin (EPO), darbepoetin, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), and platelet stimulators (e.g. eltrombopag, romiplostim, or IL-11) may continue to do so.

## 8.4 EXCLUSION CRITERIA

Patients meeting any of the following exclusion criteria are not eligible to enroll in this study:

1. Smoldering MM.
2. Plasma cell leukemia.
3. MM that does not express M-protein or FLC (i.e., non-secretory MM is excluded; plasmacytomas without M-protein or FLC are excluded).
4. Documented systemic amyloid light chain amyloidosis.
5. Active CNS MM.
6. Pregnancy or breastfeeding.
7. Radiation, chemotherapy, or immunotherapy or any other anticancer therapy  $\leq 2$  weeks prior to Cycle 1 Day 1, and radio-immunotherapy 6 weeks prior to Cycle 1 Day 1.
8. Not adequately recovered from the side effects of previous antineoplastic agents prior to dosing.
9. Active graft versus host disease after allogeneic stem cell transplantation.
10. Life expectancy of < 4 months.
11. Major surgery within four weeks prior to Cycle 1 Day 1.
12. Unstable cardiovascular function:
  - a. Symptomatic ischemia, or
  - b. Uncontrolled clinically-significant conduction abnormalities (e.g., patients with ventricular tachycardia on antiarrhythmics are excluded; patients with 1st degree

- 
- atrioventricular (AV) block or asymptomatic left anterior fascicular block/right bundle branch block (LAFB/RBBB) will not be excluded), or
- c. Congestive heart failure (CHF) of New York Heart Association (NYHA) Class  $\geq 3$ , or
  - d. Myocardial infarction (MI) within 3 months.
- 13. Uncontrolled hypertension.
  - 14. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to first dose.
  - 15. Known HIV seropositive.
  - 16. Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface antigen).
  - 17. Prior malignancies except resected basal cell carcinoma or treated cervical carcinoma *in situ*. Cancer treated with curative intent  $> 5$  years previously and without evidence of recurrence will be allowed. Cancer treated with curative intent  $< 5$  years previously will not be allowed unless approved by the medical monitor.
  - 18. GI dysfunction interfering with the ability to swallow tablets, or any GI dysfunction that could interfere with absorption of study treatment.
  - 19. Grade  $\geq 2$  peripheral neuropathy at baseline (within 14 days prior to Cycle 1 Day 1).
  - 20. Serious psychiatric or medical conditions that, in the opinion of the investigator, could interfere with treatment.
  - 21. Participation in an investigational anti-cancer study within 3 weeks prior to receiving first dose of study drug.

## 8.5 SCREEN FAILURES

Patients who sign an informed consent form and do not receive study treatment are defined as screen failures. For all screen failures, the investigator will enter the screening number, patient initials; and reason(s) for screen failure onto electronic case report forms (eCRFs). These data will also be retained in the investigator's study files and can be printed by the site in log format at the end of the study. Screen failures will be replaced. Screen failures may be re-screened.



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## 9 STUDY PLAN AND PROCEDURES

Study procedures are described in *Table 1.1*, *Section 9.2* (below), *Section 10*, and *Section 12*.

### 9.1 STUDY PATIENT NUMBER

Each patient will be assigned a unique study number and will keep this number for the duration of the study. Patient numbers will not be reassigned or reused for any reason. Patients will be identified to the Sponsor only by their assigned number, initials, date of birth, and sex. The investigator must maintain a patient master log.

### 9.2 STUDY DAY PROCEDURES

#### 9.2.1 Screening (Day -14 to Day -1)

Appropriate study procedures will be performed within 14 days prior to the start of therapy, as specified in *Table 1.1*. (Procedures may be performed during one or more visits.) The investigator should not repeat procedures completed as standard of care (SOC) if they are within the screening window and prior to signing the Informed Consent Form (ICF). Data from SOC procedures are part of the medical history and may be used for study purposes. These data include:

- Sign written informed consent (note age on day consent signed)
- Demographics (date of birth, age, gender, race, and ethnicity)
- Complete medical history for MM
- Current medical conditions (including MM baseline symptoms)
- Echocardiogram (ECG) or multiple gated acquisition (MUGA) scan
- 12-lead electrocardiogram (ECG)
- Full ophthalmological and visual acuity examination, including slit lamp examination for cataracts or other abnormalities (see *Table 1.1*)
- Baseline Disease Assessments:
  - Bone marrow biopsy for assessment of MM involvement, MM classification and karyotyping within two weeks prior to first dose
  - Serum protein electrophoresis
  - 24-hour urine protein electrophoresis
  - Free light chain
  - Skeletal survey
- Concomitant medications
- Review of inclusion and exclusion criteria
- Height and weight

- 
- Body Surface Area (BSA) will be calculated according to Dubois (*Dubois 1916*) or Mosteller (*Mosteller 1987*)
  - Vital signs (blood pressure [BP], pulse, and temperature)
  - Complete physical exam (PE) and ECOG Performance Status (Oken 1982; *Appendix 1*)
  - Urinalysis (with dipstick and microscopy, if clinically indicated)
  - Complete blood count (CBC) with differential
  - Complete serum chemistry
  - Thyroid-stimulating hormone (may be obtained with serum chemistry)
  - Coagulation tests
  - $\beta$ 2-microglobulin and quantitative immunoglobulin levels
  - Serum human chorionic gonadotropin (hCG) pregnancy test (for women of childbearing potential) within 3 days prior to first dosing with study treatment
  - QoL questionnaire (FACT-MM; *Appendix 4*)
  - Nutritional consultation
  - Randomization (must occur on Day -3 to -1)

### **9.2.2 Cycle 1 (Days 1-28)**

The following procedures will be performed pre-dose on Days 1, 8, and 15 ( $\pm 1$  day), except where indicated below:

- Weight
- Medical history review at baseline prior to first dosing with study treatment
- Vital signs (BP, pulse, and temperature)
- Symptom-directed PE
- Current medical conditions
- ECOG performance status assessment (Day 1 only)
- Oxygen saturation (pulse oximetry) pre-dose (Day 1 only)
- Urinalysis (with dipstick and microscopy, if clinically indicated) (Day 1 only)
- CBC with differential (Day 1 only)
- Complete serum chemistry (Day 1 only)
- Limited serum chemistry (Days 8 and 15)
- Serum protein electrophoresis during (screening or pre-dose Day 1 only)

- 24-hour urine protein electrophoresis (performed one time only between Day –4 and Day 1 )
- Free light chain, if relevant (screening or pre-dose Day 1 only)
- C-reactive protein (Day 1)
- Selinexor dosing in clinic on Days 1, 8, and 15, and at home on Days 3, 10, and 17. Dexamethasone without selinexor on Day 22 (in clinic) and Day 24 (at home).
- Blood draws for PK and PDn testing (see footnotes in *Table 1.1* and *Table 10.1* for information on timing)
- AEs
- Concomitant medications

#### **9.2.2.1 Cycle 1 Day 3 (+1 day) Telephone Contact**

A telephone contact with patient to evaluate supportive care medications and AEs, and to adjust supportive care as appropriate. The telephone contact with the patient should take place on Day 3 following selinexor dosing on Day 1.

#### **9.2.3 Cycles $\geq 2$**

The dose level for an individual patient ( $BSA \geq 1.4 \text{ m}^2$ ) may be increased, based on efficacy considerations AFTER a minimum of 2 cycles of study therapy. Blood sampling for PK and PDn correlative studies [as requested for Cycle 1 Day 1] will be repeated on the first day of dose escalation.

- Weight
- Vital signs (BP, pulse, and temperature)
- Symptom-directed PE
- Current medical conditions
- ECOG performance status assessment (Day 1 of each cycle)
- 12-lead ECG (Day 1 of each cycle)
- Urinalysis (with dipstick and microscopy, if clinically indicated)
- CBC with differential (Day 1 of each cycle)
- Complete serum chemistry (Day 1 of each cycle)
- Limited serum chemistry (Day 15 of each cycle)
- Coagulation tests (Day 1 of each cycle)
- Serum protein electrophoresis (Day 1 of each cycle)
- 24-hour urine protein electrophoresis (Day 1 of each cycle)

- Free light chain (Day –4 to Day 1 of each cycle)
- $\beta$ 2-microglobulin and quantitative immunoglobulin levels (Day 1 of each odd numbered cycle, starting with Cycle 3)
- C-reactive protein (Day 1 of each cycle)
- Skeletal survey (every 2 cycles, starting with Cycle 2, or as clinically indicated)
- Study drug dosing in clinic on Days 1, 8 and 15 and at home on Days 3, 10, and 17.
- Blood draw for PK and PDn testing (see footnotes in *Table 1.1* and *Table 10.1* for information on timing of blood draws)
- QoL questionnaire (FACT-MM) on Day 1 of each cycle.
- AEs
- Concomitant medications

#### **9.2.4 End-of-Treatment (EoT) Visit**

Study procedures will be performed at 30 days ( $\pm 7$ ) after the last dose of study medication for all patients, including early termination patients, as specified in *Table 1.1*.

- Weight
- Vital signs (BP, pulse, and temperature)
- Complete PE
- Current medical conditions (including MM)
- ECOG performance status assessment
- Full ophthalmological and visual acuity examination, including slit lamp examination for cataracts or other abnormalities (see *Table 1.1*)
- 12-lead ECG
- Urinalysis (with dipstick and/or microscopy, if clinically indicated)
- CBC with differential
- Complete serum chemistry
- Thyroid-stimulating hormone
- Coagulation tests
- Serum protein electrophoresis
- 24-hour urine protein electrophoresis
- Free light chain
- Serum pregnancy test (for women of childbearing potential)

- QoL questionnaire (FACT-MM)
- AEs
- Concomitant medications
- Antineoplastic therapy after end of study treatment

### 9.2.5 Survival Follow-Up

After treatment discontinuation, a telephone call will be made to the patient (or the patient's family) every 3 months to inquire about the patient's MM status, general health, and information on any antineoplastic therapies utilized since discontinuation of study treatment.

## 9.3 CONCOMITANT MEDICATIONS

### 9.3.1 Restricted Medications

*Alcohol:* Alcohol (ethanol) should be avoided on selinexor dosing days as it may compete for glutathione mediated metabolism.

*Medications:* Acetaminophen on days of selinexor dosing will not exceed a total daily dose of 1 gram. Acetaminophen use on other days is not restricted (see Prohibited Medications, below).

Patients should not take glutathione (GSH)-, S-adenosylmethionine (SAM)-, or N-acetylcysteine (NAC)-containing products during their participation in this study as these products may enhance the metabolism of selinexor. Please see *Appendix 9* for a list of representative products.

*Diet:* There are no dietary restrictions on this study. Patients should maintain adequate caloric and fluid intake.

### 9.3.2 Prohibited Medications

*Concurrent therapies:* Concurrent therapy with glucocorticoids as specified herein is allowed. Concurrent therapy with any other approved or investigative anticancer therapeutic is not allowed. Other investigational agents should not be used during the study. Use of any immunosuppressive agents during the study must be confirmed by the Medical Monitor.

*Alcohol:* Ethanol should be avoided on selinexor dosing days as it may compete for glutathione (GSH)-mediated metabolism.

*Medications:* Although acetaminophen (paracetamol) use in combination with selinexor was restricted in previous selinexor studies based on theoretical interactions with GSH, ongoing clinical safety evaluations on the use of these drugs together have not shown any significant clinical or laboratory abnormalities with doses of acetaminophen of up to 1 gm and selinexor up to 55 mg/m<sup>2</sup> (approximately 80-100 mg). Therefore, there are no

longer any restrictions on the use of acetaminophen or acetaminophen-containing products in combination with selinexor, EXCEPT on days of selinexor dosing, when acetaminophen must not exceed a total daily dose of 1 gram.

Patients should not take glutathione (GSH)-, S-adenosylmethionine (SAM)-, or N-acetylcysteine (NAC)-containing products during their participation in this study as these products may enhance the metabolism of selinexor. Please see *Appendix 9* for a list of representative products. Patients must report all prescription and non-prescription medicines to their physicians during this study.

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## 10 METHODS OF ASSESSMENT AND ENDPOINTS

### 10.1 DEMOGRAPHIC DATA

During screening, patient demographic data will be collected. These data include year of birth, age, gender, race, and ethnicity.

### 10.2 MEDICAL HISTORY

During screening, a complete medical history will be obtained from each patient. Medical history includes baseline symptoms as well as a detailed history of prior procedures for MM and other prior cancer therapies (i.e., chemotherapy, hormonal therapy, immunotherapy, biotherapy, radiotherapy, and surgery) including start and stop dates, best response, disease progression during or after therapy, as well as discontinuations due to intolerability or toxicity. Smoking history will be recorded. Data will be reviewed at Cycle 1 Day 1 (baseline; predose).

### 10.3 CONCOMITANT MEDICATIONS

Concomitant medications will be documented for each patient at each scheduled visit. A detailed history of medications will be documented during Screening (baseline) and Cycle 1 Day 1. Subsequently, at each study visit, patients will be asked whether they have taken any medication other than the study medication (from screening through the end of the study). All concomitant medications including dietary supplements, over-the-counter medications, and oral herbal preparations, as well as changes in medication, will be recorded on the eCRFs.

Supportive care (such as appetite stimulants, anti-emetics, and anti-diarrheals, etc.) is encouraged (see *Section 12.4.2*).

### 10.4 PHYSICAL EXAMINATION AND ECOG SCORE

Full PE evaluations during Screening and the EoT Visit should include general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and neurological examinations. All other PEs during the study should be symptom-directed PEs, which include body systems as appropriate.

PEs, unless otherwise noted, will include the following:

- Height (without shoes) in centimeters (cm) measured during Screening only
- Body weight (indoor clothing without shoes) in kilograms (kg)
- Body temperature
- Systolic and diastolic BP and pulse rate measured at each visit after the patient has been in a supine or sitting position for 5 minutes. BP should be assessed on the same arm at each visit.

Information about the PE must be present in the source documentation at the study site. The results of the PE prior to the start of study dosing must be included on the Relevant Medical History/Current Medical Conditions eCRF. Clinically relevant findings made after the start of Sel-Dex dosing, which meet the definition of an AE, must be recorded on the AE eCRF.

An ECOG Score Assessment (see *Appendix 1*) will be performed during Screening and Day 1 of every cycle.

## 10.5 SKELETAL SURVEY

A skeletal survey will be performed during Screening and every 2 cycles thereafter (i.e., Cycles 2, 4, etc.), or as clinically indicated. The skeletal survey should include a lateral radiograph of skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri.

## 10.6 SAFETY ASSESSMENTS

Safety evaluations will be conducted at Cycle 1 Day 1 (baseline) and on Day 1 of each remaining week of Cycle 1, Days 1 and 15 for Cycles  $\geq 2$ , and the EoT Visit. These evaluations will include a PE, an ECOG score assessment, and a 12-lead ECG (Day 1 of each cycle only and Final Study Visit, unless otherwise clinically indicated).

A standard 12-lead ECG will be performed during Screening and at the EoT Visit. Patients must rest for at least 5 minutes prior to the ECG recording. The investigator will interpret the ECG using one of the following categories: normal, abnormal but not clinically significant, or abnormal and clinically significant. The date and time the ECG was performed and the following parameters will be recorded in the eCRF: heart rate, PR interval, QT interval, QRS interval, and QT corrected using Bazett's formula.

An echocardiogram or multiple gated acquisition (MUGA) scan to assess baseline cardiac function and risk of cardiac dysfunction, including cardiomyopathy will be conducted during Screening.

An ophthalmologic assessment will be conducted by an ophthalmologist during Screening, at other visits if clinically indicated, and at the EoT Visit. The full ophthalmologic assessment includes, prior to dilation: best corrected visual acuity, slit lamp examination including tonometry; and following dilation: fundoscopy and slit lamp to document lens clarity – if a cataract is seen during the examination, the cataract will be graded according to the Lens Opacities Classification System (LOCS III) (*Appendix 6*).

The following clinical laboratory tests will be performed:

- Hematology (blood sample: ethylenediaminetetraacetic acid [EDTA]) tests including hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, WBC count, WBC differential, red blood cell count, lymphocytes, monocytes, neutrophils, band neutrophils, eosinophils, basophils, and platelets will be performed during Screening, Day 1 of each cycle, and the EoT visit. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated.
- Serum Chemistry (blood sample: serum)
  - Complete Serum Chemistry for baseline (Screening), Day 1 of each Cycle, and EoT Visit will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline



- phosphatase, total bilirubin, LDH, total protein, albumin, amylase, lipase, creatine kinase and uric acid.
- Limited Serum Chemistry, performed on Cycle 1 Days 8, 15, and 22 and  $\geq$  Cycles 2 Day 15 will include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin and LDH, unless otherwise clinically indicated.
  - If the total bilirubin concentration is increased  $> 1.5 \times \text{ULN}$ , total bilirubin should be differentiated into the direct and indirect reacting bilirubin.
  - Thyroid-stimulating hormone for baseline (Screening), Day 1 of each cycle, and EoT Visit
- Coagulation parameters evaluated during Screening and EoT Visit will include prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT).
  - Urinalysis performed during Screening, Cycle 1 Day 1, and EoT Visit will include appearance, color, urine bilirubin, glucose, hemoglobin, ketones, pH, protein, specific gravity, and urobilinogen. Microscopy will only be performed if clinically indicated.

Blood chemistry will be analyzed at each trial center by a certified local laboratory and a report of the laboratory values will be sent to the investigator. The investigator or designee will review the laboratory results and assess the clinical significance of all abnormal values. Appropriate action will be taken for any clinically significant abnormal values. Values will be documented on the laboratory report until stabilized, or the laboratory value returns to a clinically acceptable range (regardless of relationship to study medication) or baseline. Any laboratory value that remains abnormal at the Final Study Visit and that is considered clinically significant will be followed according to accepted medical standards for up to 30 days or until resolution of the abnormality or return to baseline. Toxicity will be assessed using the CTCAE version 4.03.

## 10.7 PHARMACOKINETIC AND PHARMACODYNAMIC PROCEDURES

### 10.7.1 Blood Sampling and Processing

PK and PDn sampling will be done as summarized in *Table 1.1* and *Table 10.1*. Please note that if a patient's dose is increased (as described in *Section 9* and *Section 12.1.3*, blood sampling for PK and PDn correlative studies (as requested for Cycle 1 Day 1) will be repeated on the first day of dose escalation with time points as described for Cycle 1 Day 1. Blood draws (2 mL each) for PK and PDn analyses will be performed at the following times relative to in-clinic study drug dosing:

#### CYCLE 1

- Day 1: 0 (predose), 1, 2, and 4\* hours postdose ( $\pm 10$  min for each time point)
- Day 8: 0 (predose) and 1 hour postdose ( $\pm 10$  min)
- Day 15: 0 (predose) and 1 hour postdose ( $\pm 10$  min)

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## CYCLE 2

- Day 1: 0 (predose), 1, 2 and 4\* hours postdose ( $\pm$  10 min for each time point)

\*If possible, an additional blood sample beyond the 4-hour postdose will be collected just prior to patient discharge on Day 1 of Cycles 1 and 2, provided discharge time is at least 1 hour after collection of the previous sample. This sample will be labeled “pre-discharge Day 1”; the time of blood collection will be recorded in the study data.

If a clinic visit intended to include PK/PDn sampling occurs on a non-dosing day, PK/PDn sampling for that visit will not be performed.

## 10.8 PHARMACOKINETIC ENDPOINTS

Pharmacokinetic endpoints to be evaluated include selinexor maximum plasma concentration and time-to-peak plasma concentration.

Plasma samples will be analyzed via a validated high performance liquid chromatography/tandem mass spectrometry (HPLC/MS-MS) method for plasma selinexor. Selinexor concentration data will be analyzed in a non-linear mixed effects population PK model with potential covariates including, but not limited to: age, body weight, gender, disease state, baseline hepatic or renal function, and concomitant medications. Measurements of selected plasma protein levels may be added as covariates in the PK analysis in order to investigate potential PK/PDn relationship. Details of the population PK analysis, including software, post-processing and statistical analysis, will be outlined in a separate Data Analysis Plan, to be completed prior to database lock.

**Table 10.1 Collection Time Points and Blood Volumes for PK and PDn**

Time Point	Total Volume of Blood (mL)	NUMBER OF TUBES BY VOLUME OF BLOOD				
		PK	PDn Predictive Biomarkers	PDn Plasma Protein and cytokines	PDn RNA from whole blood	Bone Marrow Biopsy**
		1 tube x 2 ml	3 tubes x 4 ml	1 tube x 2 ml	2 tubes x 2.5 ml	1 tube x 6 ml
<b>Cycle 1 Day 1</b> (repeat if patient dose escalates)						
Predose (< 10 min before dosing)	21	1 x 2 ml	3 x 4 ml	1 x 2 ml	2 x 2.5 ml	1 x 6 ml
1 hr (± 10 min) postdose	2	1 x 2 ml				
2 hr (± 10 min) postdose	2	1 x 2 ml				
4 hr (± 10 min) postdose	9	1 x 2 ml		1 x 2 ml	2 x 2.5 ml	
Pre-Discharge*	2	1 x 2 ml				
<b>Cycle 1 Day 8</b>						
Predose (< 10 min before dosing)	2	1 x 2 ml				
1 hr (± 10 min) postdose	2	1 x 2 ml				
<b>Cycle 1 Day 15</b>						
Predose (< 10 min before dosing)	2	1 x 2 ml				
1 hr (± 10 min) postdose	2	1 x 2 ml				
<b>Cycle 2 Day 1</b>						
Predose (< 10 min before dosing)	2	1 x 2 ml				
1 hr (±10 min) postdose	2	1 x 2 ml				
2 hr (±10 min) postdose	2	1 x 2 ml				
4 hr (± 10 min) postdose	2	1 x 2 ml				
Pre-Discharge*	2	1 x 2 ml				

\*If possible, an additional blood sample beyond the 4 hour post-dose will be collected just prior to patient release from the clinic on Day 1 of Cycles 1 and 2, provided that time is ≥ 1 hour after collection of the previous sample. This sample will be labeled “pre-discharge Day 1” and the time of blood collection will be recorded in the CRF.

\*\*Not included in total volume of blood

## 10.9 SUPPORTIVE AND EXPLORATORY STUDIES

Portions of the bone marrow biopsy at pre-screening or screening will be used for supportive efficacy and exploratory studies. Analyses of cancer-related signaling molecules and pathways will be conducted by the sponsor. Details of sample collection and processing can be found in the study lab manual.

### 10.9.1 Supportive Efficacy Endpoints

ORR, DOR, PFS, CBR, DCR, and OS of Sel-Dex in patients with MM will be assessed.

Comparison of each patient's Sel-Dex TTP with the TTP of his/her most recent prior therapy will also be made.

These comparisons are not meant to be comprehensive but rather provide a high level overview of the supportive efficacy research to be undertaken.

## **10.9.2 Exploratory Pharmacodynamic Studies**

### **10.9.2.1 Plasma Proteins and Cytokines**

Blood samples will be collected pre- and post-dosing and analyzed for plasma cytokine concentrations. Cytokines may include: interleukin 1 alpha (IL1 $\alpha$ ), tumor necrosis factor alpha (TNF $\alpha$ ), interleukin 6 (IL-6), monocyte chemoattractant protein-1 (MCP1), interferon gamma (IFN $\gamma$ ), vascular endothelial growth factor alpha (VEGF $\alpha$ ), interleukin 8 (IL-8), interferon alpha (IFN $\alpha$ ), interleukin 10 (IL-10).

### **10.9.2.2 Gene Expression Changes in Whole Blood RNA**

Peripheral blood and/or bone marrow samples collected on Cycle 1 Day 1 (pre-dose) will be used to obtain non-tumor and CD138+/CD138- tumor cell fractions by fluorescence-activated cell sorting (FACS). RNA/DNA will be used for comparative whole exome sequencing (WES) and transcriptomic analyses to identify predictive biomarkers of selinexor response.

### **10.9.2.3 Gene Expression Changes in RNA from Whole Blood**

Patient blood samples will be collected pre- and post-dosing ( $\geq 4$  hr) on C1 D1 and processed to isolate total RNA. RNA will be used to study changes in gene expression after exposure to selinexor. Changes in mRNA of genes which are up/down-regulated once XPO1 is inactivated will be assessed by quantitative real time polymerase chain reaction (qRT PCR). RNA from these blood samples may be subjected to deep RNA sequencing correlative studies.

### **10.9.2.4 Bone Marrow Biopsies for Genomic, Transcriptomic and FISH Analyses**

Fresh bone marrow biopsies (6 ml) will be used to obtain non-tumor CD138- and tumor CD138+ cell fractions by fluorescence-activated cell sorting (FACS). RNA/DNA will be used for comparative whole exome sequencing (WES) and transcriptomic analyses to identify predictive biomarkers of selinexor response. In addition, tumor cells will be used to assess the presence of the high risk mutations P5317D Deletion and 14-16 and 4-14 translocations. Cytogenetic analysis by FISH will be done to identify specific chromosomal translocations at sites known to show rearrangements in MM.

## **10.10 EFFICACY PROCEDURES**

### **10.10.1 Objective Disease Assessment**

The following procedures will be performed for disease assessment:

- Serum Protein Electrophoresis (Screening and Day 1 of every Cycle  $\geq 2$ , when relevant)

- Urine Protein Electrophoresis (Screening and Day 1 of every Cycle  $\geq 2$ , when relevant)
- Free Light Chain (Screening and Day 1 of every cycle, when relevant)
- Skeletal survey (Screening and every 2 cycles  $\geq$  Cycle 2, or as clinically indicated)
- $\beta_2$ -microglobulin and quantitative immunoglobulin levels (Day 1 of odd numbered cycles)
- Bone marrow aspirates and/or biopsies will be taken within 2 weeks prior to C1 D1, first dose (baseline) to assess bone marrow involvement, MM classification and karyotyping. The bone marrow biopsy will be repeated 1 week prior to C2 D1 and whenever clinically indicated to confirm CR only in those patients who had MM known bone marrow involvement prior to dosing.

## 10.11 EFFICACY ENDPOINTS

ORR is the primary efficacy variable for the study, with supportive information obtained from the duration of ORR.

Secondary efficacy variables will include the following, assessed according to the definitions presented in *Section 6.2*:

- DOR for each study regimen
- CBR, with supportive information from duration of CBR
- DCR, with supportive information from duration of DCR
- PFS
- OS
- Assessment of quality of life using FACT-MM Questionnaire

### 10.11.1 Response Criteria

Disease response will be assessed by the IMWG Response Criteria for MM (*Kyle 2009*) in patients on Cycle 3 Day 1 and every 2 months of therapy thereafter until disease progression or death. There is no maximum treatment duration.

Definitions of the individual Response Criteria are provided in *Appendix 3*.

### 10.11.2 Quality of Life Assessments

Health-related QoL and potential for improvement over the course of the study will be assessed by the FACT-MM patient-reported outcome questionnaire that is specifically relevant to MM (*Appendix 4*).

Patients should complete the QoL assessment during screening, on Day 1 of each cycle  $\geq$  Cycle 2, and the EoT visit preferably *before* they undergo any study related procedure, including other study related evaluations, discussions with medical personal, physician and study treatment administration.

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## 11 DISCONTINUATION CRITERIA

### 11.1 EARLY DISCONTINUATION OF THE STUDY

The study may be discontinued at the sole discretion of the Sponsor for any reason, including medical or ethical reasons affecting the continued performance of the study, or difficulties in the recruitment of patients.

The DSMB will inform the sponsor if futility is declared (see *Section 7.2*). The sponsor, in conjunction with appropriate regulatory authorities, would then decide if the trial should be modified or terminated. If this occurs, the sponsor will notify IRBs and investigators.

### 11.2 EARLY DISCONTINUATION OF INDIVIDUAL PATIENTS

The investigator may remove a patient from study treatment at his/her discretion for any of the following reasons:

- Disease progression defined according to IMWG Uniform Response Criteria for progression of MM
- Unacceptable AE(s) or failure to tolerate the study treatment
- Patient decides to discontinue study therapy
- Any medically appropriate reason or significant protocol violation, in the opinion of the investigator

Patients may discontinue study treatment for any reason. Patients who elect to discontinue study treatment should be encouraged to continue in the study so that follow-up information on disease progression and survival status may be obtained. However, patients may elect to withdraw consent and decline further participation in the trial.

All patients will be followed until disease progression, withdrawal of consent, occurrence of any withdrawal criteria, intolerable toxicity precluding further treatment with study drug, death, or loss to follow up.

## 12 TREATMENT

Selinexor study medication will be in the form of a coated, immediate-release tablet for oral administration. Selinexor tablets will be supplied as either (a) single-strength (20 mg) tablets in wallet-size blister packs, or (b) 10 mg and 25 mg tablets in multi-dose vials of 50 tablets. Dexamethasone (20 mg) will be given with each dose of selinexor during Weeks 1-3, and without selinexor during Week 4. Dexamethasone will not be included in selinexor blister packs. For patients with intolerance to glucocorticoids, a minimum dose of 10 mg dexamethasone is permitted. Where possible, dexamethasone will be obtained by the Investigator (preferred), however when necessary it will be provided by the sponsor.

## 12.1 DOSING AND ADMINISTRATION

### 12.1.1 Labeling

All drug containers will be labeled in accordance with current International Conference on Harmonization (ICH), GCP, and regulatory agency-specific requirements (e.g. FDA, MHRA). Medication labels will include the medication name, storage conditions, and batch number, and will comply with language and legal requirements of the US.

### 12.1.2 Dosing Information

Selinexor will be administered as a fixed oral selinexor dose of 80 mg twice weekly (e.g., Monday and Wednesday or Tuesday and Thursday, etc.) on Weeks 1, 2, and 3 of each 4-week cycle. No doses of selinexor will be given during Week 4. For doses on non-clinic days during Weeks 1-3, the patient will be provided with doses by the hospital pharmacy to take home.

Dexamethasone (20 mg) will be given with each dose of selinexor. Dexamethasone will also be given at the same dose and schedule during Week 4 of every cycle. For patients with partial intolerance to glucocorticoids (as determined by the Investigator), a minimum dose of 10 mg dexamethasone is permitted. Dexamethasone will be provided to take home in the form of tablets.

In select cases (e.g., for patients showing stable disease or partial response and tolerating treatment particularly well), the selinexor dose may be increased by 20 mg after discussion with the sponsor. The dose level for an individual patient may be escalated based on efficacy considerations after a minimum of 2 cycles of study therapy. However, in no case may the dose for any patient exceed 70 mg/m<sup>2</sup>. Prior to any potential dose increase, the BSA for the patient will be calculated. Patients with may have their dose increased if it would result in a dose >70 mg/m<sup>2</sup>. Blood sampling for PK and PDn correlative studies (as requested for Cycle 1 Day 1) will be repeated on the first day of dose escalation.

Selinexor should be given with, or within 30 minutes of, solid food consumption together with at least 120 mL (4 ounces) of fluids (water, juice, etc.) For details of drug formulation, preparation, and administration, please refer to *Appendix 5*.

Selinexor tablets should be swallowed whole and should not be crushed to avoid increased risk of dermatologic toxicity if the powder comes in contact with skin.

Compliance to study medication will be assessed by the investigator or delegate at each patient visit and recorded in source documents after discussion with the patient and drug accountability. The date will be recorded as per study drug schedule. The Principal Investigator (PI) or the designee will account for the number of tablets dispensed against those returned by the patient. Any deviations and missed doses will be recorded in the eCRF and drug accountability logs for verification with the reasons. The investigator / designee will attempt to ensure complete compliance with the dosing schedule by providing timely instructions to the patients.

### 12.1.3 Dosing Instructions for Patients who Achieve CR

In an effort to improve long-term disease control and tolerability, this protocol allows for dose reductions in patients with very good anti-tumor activity of selinexor. Thus, for patients who achieve  $\geq$  VGPR for  $\geq$  6 months and who, in the opinion of the investigator may benefit from dose reduction(s), the following modifications may be considered: (a) The dose of dexamethasone may be reduced by 40% or (b) the dose of selinexor may be reduced by 20 mg or (c) the frequency of selinexor may be reduced to once weekly. In general, dexamethasone should always be given on the day(s) of selinexor dosing. Patients whose doses are reduced under this schema should have appropriate MM markers monitored at least every two weeks (e.g., with FLC) so that dose may be re-escalated to their initial dose if evidence of progression occurs. These monitoring studies may be done at local laboratories.

### 12.1.4 Dose Reduction Guidelines

Toxicity will be graded according to CTCAE criteria; the therapy modifications described below are applied according to this severity grading.

If more than one different type of toxicity occurs concurrently, the most severe grade will determine the modification.

Re-escalation of the study drug is allowed as outlined in the sections that apply for the specific toxicity. If drug-related toxicity requires a treatment delay of more than 28 days, the patient is taken off protocol treatment.

Each dose modification or treatment delay must be documented, including the respective reason.

Based on observations from the ongoing Phase 1 studies in patients with advanced hematological and solid tumors, selinexor shows a reasonably wide therapeutic range, with activities from  $\sim 6$  mg/m<sup>2</sup> to  $\geq 60$  mg/m<sup>2</sup>. Therefore, in order to optimize specific anti-tumor activity and the patient's tolerability, dose reductions and/or schedule modifications will be allowed as described in *Tables 12.1* and *12.2*. Patients should also be treated aggressively with supportive care to reduce toxicities.

For all  $\geq$  Grade 3 hematological or non-hematological AEs that are NOT selinexor related, after consultation with the Medical Monitor and at the discretion of the Investigator, selinexor dosing may be maintained, provided that the patient can continue to take the agent by mouth.

**Table 12.1 Pre-specified Dose/Schedule Modifications for Adverse Events Related to Study Drug**

Dose Level	Preferred Schedule Selinexor Dose
Dose level 1	Selinexor 80 mg twice weekly (starting dose)
Dose level -1	Selinexor 60 mg twice weekly
Dose level -2	Selinexor 60 mg once weekly (with dexamethasone 40 mg as a single or divided dose)
Dose level -3	Discontinue Dosing



**Table 12.2 Dose Adjustment Guidelines for Selinexor and Dexamethasone**

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification	Dexamethasone Dose Modification
<b>Fatigue (common)</b>			
Grade 1	Rule out other causes of fatigue. Consider addition of 4-8 mg dexamethasone or equivalent on the day after selinexor. Insure adequate caloric intake and assess volume status.	Maintain dose.	Maintain dose.
Grade 2	Rule out other causes of fatigue. Consider addition of 4-8 mg dexamethasone or equivalent on the day after selinexor. Insure adequate caloric intake and assess volume status. For additional support see NCCN guidelines <sup>a</sup> .	Maintain dose. Consult medical monitor for additional option such as temporary dose reduction or short dose interruptions.	Maintain dose.
Grade 3	See guidelines for Grade 2 fatigue	Interrupt selinexor dosing until resolved to Grade $\leq 2$ . For first occurrence of Grade 3, if adequate supportive care resulted in fatigue improving to Grade $\leq 1$ within 7 days, restart selinexor at current dose. Otherwise, restart selinexor at one dose level below ( <i>Table 12.1</i> ).	Maintain dose.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification	Dexamethasone Dose Modification
<b>Anorexia or Weight loss</b>			
Grade 1	Rule out other causes of anorexia. Assess dietary options (e.g., try a variety of other foods). Add high-calorie supplements (e.g., Ensure®). Consider addition of 4-8 mg dexamethasone or equivalent on the day after selinexor.	Maintain dose.	Maintain dose.
Grade 2	Rule out other causes of anorexia. Assess dietary options (e.g., try a variety of other foods). Add high-calorie supplements (e.g., Ensure®). Consider addition of 4-8 mg dexamethasone or equivalent on the day after selinexor. Consider megestrol acetate 80-400 mg daily. Consider anabolic steroids such as oxandrolone, or dronabinol (Marinol®) or other cannabinoid, mainly for patients who can't tolerate steroids or at high risk to progress. For additional supportive care see NCCN guidelines <sup>b</sup> ( <i>Appendix 8</i> )	Selinexor may be skipped intermittently while supportive medications are instituted, usually for <1 week.	Maintain dose.
Grade 3	See guidelines for Grade 2 anorexia.	Interrupt dosing with selinexor. Restart selinexor at 1 dose level reduction ( <i>Table 12.1</i> ) once anorexia resolves to Grade ≤ 2 and patient is clinically stable.	Maintain dose.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification	Dexamethasone Dose Modification
Grade 4 (anorexia only)	See guidelines for Grade 2 anorexia.	Stop dosing of selinexor. Restart selinexor at 1 dose level reduction ( <i>Table 12.1</i> ) only if anorexia resolves to Grade $\leq 2$ , patient is clinically stable other contributing factors have been addressed.	Maintain dose.
<b>Nausea/ - acute (common)</b>			
Grade 1	Insure adequate caloric intake and assess volume status. Consider alternate 5-HT3 antagonists and/or D2 antagonists as needed. Consider addition of NK1 antagonists. Consider addition of 4-8 mg dexamethasone or equivalent on the day after selinexor.	Maintain dose.	Maintain dose.
Grade 2	See guidelines for Grade 1 nausea. For additional options see NCCN guidelines for antiemesis <sup>c</sup> ( <i>Appendix 8</i> )	Selinexor may be skipped intermittently while supportive medications are instituted, usually for <1 week.	Maintain dose.
Grade 3	See guidelines for Grade 1 nausea For additional options see NCCN guidelines for antiemesis <sup>c</sup> ( <i>Appendix 8</i> ).	Interrupt selinexor dosing until resolved to Grade $\leq 2$ , For first occurrence of Grade 3, if adequate supportive care resulted in nausea improving to Grade $\leq 1$ within 3 days, restart selinexor at current dose. Otherwise, restart selinexor at one dose level below ( <i>Table 12.1</i> ). If nausea stabilizes for at least 4 weeks at Grade $\leq 1$ , then original dose of selinexor may be resumed.	Maintain dose.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification	Dexamethasone Dose Modification
<b>Hyponatremia (common)</b>			
Grade 1 (sodium levels <Normal to 130 nM)	Be certain sodium level is corrected for hyperglycemia (serum glucose >150mmol/L). Rule out other causes of low sodium (e.g., cardiac, hepatic, adrenal, renal and thyroid diseases, SIADH, Fanconi Syndrome, hyperglycemia, diuretic use). Consider salt supplementation one – two times per day.	Maintain dose.	Maintain dose.
Grade 3 (sodium levels 126-129nM) without Symptoms	Be certain sodium level is corrected for hyperglycemia (serum glucose >150mmol/L). Rule out other causes of low sodium (e.g., cardiac, hepatic, adrenal, renal and thyroid diseases, SIADH, Fanconi Syndrome, hyperglycemia, diuretic use). Initiate salt supplementation two-three times per day.	Hold selinexor until Grade $\leq 1$ ( $\geq 130$ nM), restart on the same dose level.	Maintain dose.
Grade 3 (120-125 nM) or Grade 4 or any Grade 3 with Symptoms	Correct sodium as per institutional guideline Initiate salt supplementation two-three times per day.	Hold selinexor until resolved to Grade $\leq 1$ ( $\geq 130$ nM) then reduce selinexor dose by 1 level ( <i>Table 12.1</i> ). For Grade 3 hyponatremia, if serum sodium stabilizes to grade $\leq 1$ for at least 4 weeks, then original dose of selinexor may be resumed.	Maintain dose.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification	Dexamethasone Dose Modification
<b>Diarrhea (common)</b>			
Grade 1+2	Diet recommendation as per guidelines (Benson, 2004) <sup>d</sup> . Institute standard anti-diarrheal therapy. After the first occurrence of diarrhea, loperamide 2 mg should be considered prophylactically approximately 1-2 hours before the administration of selinexor and repeated every 4 hours for the first 12 hours.	For Grade 2 only, reduce selinexor one dose level ( <i>Table 12.1</i> ), until resolved to $\leq$ Grade 1, then re-start at the current dose level.	Hold dose in the case of opportunistic infection. Dexamethasone can then be re-initiated when culture is negative.
Grade 3	Institute IV fluids Diet recommendation as per guidelines (Benson, 2004) <sup>d</sup> . Institute standard anti-diarrheal therapy. Once the symptoms resolve to $\leq$ Grade 1, loperamide 2 mg should be considered prophylactically approximately 1-2 hours before the administration of selinexor and repeated every 4 hours for the first 12 hours.	Delay selinexor until resolved to $\leq$ Grade 1, then reduce selinexor dose by one dose level ( <i>Table 12.1</i> ). If diarrhea stabilizes for at least 4 weeks at Grade $\leq$ 1, then original dose of selinexor may be resumed.	Hold dose in the case of opportunistic infection. Dexamethasone can then be re-initiated when culture is negative.
Grade 4	Rule out other causes of diarrhea, including infectious agents. In case of opportunistic infection, withdraw all steroids (with tapering if medically appropriate) until culture is negative. Follow institutional guidelines for Grade 4 diarrhea.	Delay selinexor until resolved to $\leq$ Grade 1, then reduce selinexor dose by one dose level ( <i>Table 12.1</i> ).	Hold dose in the case of opportunistic infection. Dexamethasone can then be re-initiated when culture is negative.
<b>Thrombocytopenia</b>			
Grade 1	In cases of marked reduction in platelet numbers from baseline, consider implementing platelet growth factors (eltrombopag or romiplostim +/- oprelvekin [IL-11]).	Maintain dose.	Maintain dose.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification	Dexamethasone Dose Modification
Grade 2	Strongly consider implementing platelet growth factors (eltrombopag or romiplostim +/- oprelvekin [IL-11]). Monitor platelet counts weekly.	Maintain dose.	Maintain dose, start proton pump inhibitor (PPI).
Grade 3 Thrombocytopenia Without bleeding	Initiate platelet growth factors (eltrombopag or romiplostim +/- oprelvekin [IL-11]). Monitor platelet counts at least weekly. Consider holding anti-platelet agents.	Begin (or maintain) once weekly selinexor dosing at the same dose level until resolved to Grade $\leq 2$ , then return to twice weekly dosing (if appropriate). In certain cases when there is a significant disease involvement in the bone marrow (e.g., in heavily pretreated multiple myeloma) or pre-existing compromised marrow function (e.g., due to prior marrow-toxic therapy), the Investigator in consultation with the Sponsor may decide to continue Selinexor dosing, provided that platelet counts and bleeding symptoms/signs are closely monitored.	Maintain dose, start PPI.
Grade 4 Thrombocytopenia Without bleeding	Follow guidelines for Grade 3 thrombocytopenia without bleeding. Transfuse as per institutional guidelines.	Hold dosing until Grade $\leq 3$ and follow above guidelines if Grade $> 2$ . In certain cases when there is a significant disease involvement in the bone marrow (e.g., in heavily pretreated multiple myeloma) or pre-existing compromised marrow function (e.g., due to prior marrow-toxic therapy), the Investigator in consultation with the Sponsor may decide to continue Selinexor dosing, provided that platelet counts and bleeding symptoms/signs are closely monitored.	Maintain dose, start PPI.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification	Dexamethasone Dose Modification
≥ Grade 3 Thrombocytopenia associated with bleeding	Transfuse as per institutional guidelines. Follow guidelines for Grade 3 thrombocytopenia without bleeding.	Hold selinexor dosing until platelet counts $>50,000/\text{mm}^3$ , then resume selinexor dosing at one dose level below ( <i>Table 12.1</i> ).	Maintain dose, start PPI. If any signs of gastrointestinal bleeding are detected, (e.g., suspected melena) without hemoglobin decreases, hold for one dose and restart in the same dose. Any hemoglobin reductions should be evaluated aggressively, and the role of steroids or anti-platelet agents investigated.
<b>Neutropenia</b>			
Grade 3 neutropenia without fever	Implement growth factors per institutional guidelines until neutrophils are consistently $>1,500/\text{mm}^3$ .	Maintain dose.	Maintain dose.
Grade 4 neutropenia without fever	Implement growth factors per institutional guidelines.	Reduce selinexor dose by one level ( <i>Table 12.1</i> ). After implementation of growth factors, for patients who achieve neutrophil levels $>1,500/\text{mm}^3$ for $>4$ weeks (in the presence or absence of growth factors), selinexor dose may be re-escalated, with frequent monitoring implemented.	Reduce dose by 50% until neutrophils return to Grade $\leq 3$ .
Grade 3 or 4 neutropenia with fever (febrile neutropenia)	Implement growth factors per institutional guidelines. Implement broad anti-microbial coverage per institutional guidelines. Please note that selinexor has not been associated to date with any opportunistic infections.	Hold selinexor until fever resolves and patient is clinically stable. When patient is clinically stable, restart dosing one dose level below ( <i>Table 12.1</i> ). After implementation of growth factors, for patients who achieve neutrophil levels $>1,500/\text{mm}^3$ for $>4$ weeks, selinexor dose may be re-escalated, provided frequent monitoring is implemented.	Hold dose until fever resolves and patient is clinically stable. Consider adrenal suppression when altering steroid doses. Restart the same dose of dexamethasone (if it has been tapered) after neutropenia has resolved to $>1,500/\text{mm}^3$ .

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification	Dexamethasone Dose Modification
<b>Other selinexor-related adverse events*</b>			
Grade 1 or 2	Initiate standard supportive care and follow institutional guidelines.	Maintain dose.	Maintain dose.
Grade 3	Initiate standard supportive care and follow institutional guidelines.	Delay dose until resolved to Grade $\leq 1$ or baseline, then reduce by one dose level ( <i>Table 12.1</i> ).	Delay dose given on days of selinexor dosing if selinexor dosing delayed. Resume at prior dose when selinexor dosing resumes.
Grade 4	Initiate standard supportive care and follow institutional guidelines.	Delay dose until resolved to Grade $\leq 1$ or baseline, then reduce by two dose levels ( <i>Table 12.1</i> ).	Delay dose given on days of selinexor dosing if selinexor dosing delayed. Resume at prior dose when selinexor dosing resumes.
All dose modifications should be based on the worst preceding toxicity. * Isolated values of $\geq$ Grade 3 alkaline phosphatase values will NOT require dose interruption. Determination of liver vs. bone etiology should be made, and evaluation of gamma-glutamyl transferase (GGT), 5'-nucleotidase (5'NT), or other liver enzymes should be performed.			
<sup>a</sup> National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Fatigue. Available at <a href="http://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf">http://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf</a> <sup>b</sup> National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Palliative Care, version 1.2014. Fort Washington, NY. April 2014. Available at: <a href="http://www.lls.org/content/nationalcontent/resourcecenter/freeducationmaterials/generalcancer/pdf/facts.pdf">http://www.lls.org/content/nationalcontent/resourcecenter/freeducationmaterials/generalcancer/pdf/facts.pdf</a> . <sup>c</sup> National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Antiemesis, version 2.2014. Fort Washington, NY. April 2014. Available at: <a href="http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf">http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf</a> . <sup>d</sup> Benson AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Onc 2004; 22:2918.			

#### 12.1.4.1 Selinexor Dose Reduction for Decreased Glomerular Filtration Rate (GFR)

Selinexor is not significantly eliminated by the kidney; therefore, no dose alteration of selinexor is required with renal dysfunction. Creatinine clearance must be  $> 20$  mL/min in order to initiate therapy with selinexor/dexamethasone. If creatinine clearance declines during treatment and is believed to be unrelated to selinexor, the dose of selinexor may be maintained provided that the patient's condition is closely monitored. If creatinine clearance declines to  $< 20$  mL/min and this is felt to be related to selinexor, then the selinexor dose should be reduced by one level. If creatinine clearance returns to  $> 20$  mL/min for 4 weeks, then the dose of selinexor can be returned to previous level. If dialysis is implemented during selinexor treatment, then selinexor should always be given after dialysis.



#### **12.1.4.2 Selinexor Dose Adjustment in the Setting of Infection**

Patients with active uncontrolled or suspected infections should have selinexor treatment withheld until infection has clinically resolved or the patient is clinically stabilized. Dexamethasone should be adjusted per institutional guidelines, and adrenal suppression considered. After the infection has resolved clinically, or the patient's clinical condition has stabilized, treatment with selinexor may continue at the original dose. Missed doses will not be replaced. Patients may continue on antibiotics or other anti-microbial agents for prolonged periods while re-initiating their selinexor regimen at the discretion of the investigator.

#### **12.1.4.3 Conditions Not Requiring Selinexor Dose Reduction**

The following conditions are exceptions to the dose modification guidelines. Selinexor does not need to be held in the following cases:

- Alopecia of any grade
- Electrolyte or serum analyte (e.g., urate) abnormalities that are reversible with standard interventions

#### **12.1.4.4 Missed or Vomited Doses**

Note: A maximum of 2 doses may be given per week.

##### **Missed Doses**

**If a dose was missed**, the schedule of that week should be altered to accommodate two doses in that week with at least 36 hours between two consecutive doses.

**If a dose must be skipped**, (e.g., due to recommendation of treating physician), the next dose will be taken as per schedule. Doses should not be administered less than 36 hours apart and all missed and delayed doses should be documented.

If a patient missed a full one or two-week period of dosing for non-study drug-related events (e.g., a required medical procedure or an unanticipated personal emergency), the days missed will be replaced. For example, if patient missed Cycle 2 Day 7 to Cycle 2 Day 14, then patient will start their next dosing on Cycle 2 Day 7 following the break. Similarly, if a patient misses Cycle 3 Day 1 to Cycle 3 Day 15, then the patient will start their next dosing on Cycle 3 Day 1. In this fashion, laboratory and radiographic assessments remain appropriate for timing of the administration of anti-cancer therapy.

##### **Vomited Doses**

If a dose is vomited < 1 hour of ingestion, it will be replaced. If vomiting occurs > 1 hour after dosing, it will be considered a complete dose.

#### **12.1.4.5 Dose Escalation**

Dose adjustments may be made as appropriate by the investigator (see *Section 12.1.3*). In select cases (e.g., for patients showing stable disease or partial response and tolerating treatment

particularly well), the selinexor dose may be increased by 20 mg after discussion with the medical monitor. However, in no case may the dose for any patient exceed 70 mg/m<sup>2</sup>. Prior to any potential dose increase, the BSA for the patient will be calculated. Blood sampling for PK and PDn correlative studies (as requested for Cycle 1 Day 1) will be repeated on the first day of dose escalation. Patients will be followed as long as possible or until disease progression and death.

## 12.2 STUDY DRUG STORAGE

Selinexor tablets should be stored in a locked and secured area with access restricted to the site staff pharmacist or designee(s) at or below 86°F (30°C) (i.e., room or refrigerated temperature). Room temperature storage is preferred. The tablets should not be stored at freezer temperatures or frozen.

Tablets will be supplied either in (a) polyvinyl chloride/polyethylene/polychlorotrifluoroethylene (PVC/PE/PCTFE) film blisters with a paper-backed foil in a secondary wallet with childproofing (20 mg tablets) or (b) white high density polyethylene (HDPE) bottles of 50 tablets (10 mg and 25 mg tablets). See *Appendix 5* for detailed information on selinexor preparation, storage, stability, and administration.

Dexamethasone tablets should be stored as recommended on the product label. Keep it in the container it came in, tightly closed, and out of reach of children. Store it at room temperature and away from excess heat and moisture (not in the bathroom).

## 12.3 STUDY DRUG ACCOUNTABILITY

Selinexor and, if required by the site, dexamethasone for the study will be provided by Karyopharm Therapeutics, Inc. Sites must request study drug by submitting an order form directly to the drug depot in order for the study drug to be shipped to the site pharmacy. The investigator (or designee) will verify and acknowledge receipt of all study drug shipments by signing and returning all required forms.

Study drug accountability records will be maintained at the site pharmacy and will be available for review by the study monitor during each monitoring visit and at the close out visit. The study drug must be reviewed by the clinical research associate (CRA) prior to destruction or return shipment.

Selinexor should not be used for any purpose outside the scope of this protocol, nor can selinexor be transferred or licensed to any party not participating in the clinical study. Data for selinexor are confidential and proprietary and shall be maintained as such by the investigators.

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of unused material.

All drug supplies provided by Karyopharm Therapeutics, Inc. must be kept in an appropriate, limited access, secure place until used or returned to Karyopharm Therapeutics, Inc. or designee for destruction. Drug supplies will be counted and reconciled at the site before being returned. The study site will be required to maintain a log of the temperature where the study medication is stored.

## 12.4 CONCOMITANT TREATMENTS

### 12.4.1 Required 5-HT3 Antagonists

In order to minimize nausea, unless contraindicated, all patients must receive 5-HT3 antagonists (ondansetron 8 mg or equivalent) starting before the first dose of selinexor and continued two or three times daily, as needed.

### 12.4.2 Supportive Care

Supportive measures for optimal medical care should be provided during participation in this clinical trial. Based on clinical observations in over 400 adult patients treated with selinexor as of 31 May 2014, the main side effects are primarily related to anorexia with poor caloric and fluid intake, fatigue, and nausea. Thrombocytopenia also occurs, although it is rarely associated with bleeding. Besides dexamethasone included in the standard treatment plan, and required 5-HT3 prophylaxis (*Section 12.4.1*), supportive care including anti-nausea/anti-emetic therapy, acid suppression (proton pump inhibitors [PPI] and/or H2-blockers) and other treatments may be administered as described below:

- Appetite stimulants: megestrol acetate at a dose of 80-400 mg daily.
- Centrally acting agents: per National Comprehensive Cancer Network® [NCCN] Clinical Practice Guidelines®<sup>2</sup> for antiemesis and anorexia/cachexia [palliative care]) see *Appendix 7* (antiemesis) and *Appendix 8* (anorexia), respectively.
- Neurokinin 1 receptor antagonist (NK1R antagonist): aprepitant or equivalent should be considered and will be covered for selected patients who have severe nausea and vomiting.

#### Infection

Appropriate broad-spectrum intravenous antibiotics and antifungal agents should be started immediately in patients who develop fever or other signs of systemic infection. Selinexor should be suspended in any patient with Grade 4 infection or clinical sepsis (in the absence of documented infection) until the condition is stabilized. Selinexor can then be re-started at the same dose.

#### 12.4.2.2 Other Glucocorticoid Side Effects

The management of common glucocorticoid side effects is well documented. Aggressive use of proton-pump inhibitors (PPIs), anti-hypertensives and other agents is strongly encouraged in order to maintain the use of intermittent dexamethasone in combination with selinexor in this study.

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<sup>2</sup> Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) V.2.2014. © National Comprehensive Cancer Network, Inc. 2014. All rights reserved. Accessed September 11, 2014. To view the most recent and complete version of the guideline, go online to [www.nccn.org](http://www.nccn.org). NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

Patients with documented osteopenia or osteoporosis should continue to take dexamethasone with selinexor as indicated in the study. Standard precautions such as use of bisphosphonates should be instituted unless contraindicated.

### **12.4.3 Concomitant Medication and Treatment**

Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins, dietary supplements, over-the-counter medications, and oral herbal preparations. Patients may continue their baseline medication(s). All concomitant medication(s) must be reported in the eCRF. Any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s), and any clinical findings, if applicable.

#### **12.4.3.1 Permitted Concomitant Medication**

Patients will receive concomitant medications to treat symptoms, AEs, and intercurrent illnesses that are medically necessary as standard care. Medications to treat concomitant diseases like diabetes, hypertension, etc., are allowed.

#### **Prevention of pregnancy**

Female patients of child bearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at screening, and male patients must use an effective barrier method of contraception if sexually active with a female of child bearing potential. Acceptable methods of contraception are condoms with contraceptive foam; oral, implantable or injectable contraceptives; contraceptive patch; intrauterine device; diaphragm with spermicidal gel; or a sexual partner who is surgically sterilized or post-menopausal. Total (true) abstinence (when this is in line with the preferred and usual lifestyle of the patient), is an acceptable method of contraception. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. For both male and female patients, effective methods of contraception must be used throughout the study and for 3 months following the last dose.

#### **Radiation Treatment**

If clinically indicated, palliative radiation therapy to non-target lesions is permitted but study drug should be held for  $\geq 1$  day before the start of palliative radiation therapy and  $\geq 1$  day following each dose of palliative radiation therapy. Treatment with selinexor shall not be discontinued solely due to palliative radiation.

### **12.4.4 Restrictions and Prohibitions**

#### *Concurrent therapies:*

Concurrent therapy with glucocorticoids as specified herein is allowed. Concurrent therapy with any other approved or investigative anticancer therapeutic is not allowed. Other investigational agents should not be used during the study. Use of any immunosuppressive agents during the study must be confirmed by the Medical Monitor.

Concurrent therapy with any other approved or investigative anticancer therapeutic is **not** allowed.

Use of any immunosuppressive agents during the study must be approved by the Medical Monitor prior to use.

Other investigational agents for any condition should not be used during the study.

*Alcohol:* Ethanol should be avoided on selinexor dosing days as it may compete for glutathione (GSH)-mediated metabolism.

*Medications:* Although acetaminophen (paracetamol) use in combination with selinexor was restricted in previous selinexor studies based on theoretical interactions with GSH, ongoing clinical safety evaluations on the use of these drugs together have not shown any significant clinical or laboratory abnormalities with doses of acetaminophen of up to 1 gm and selinexor up to 55 mg/m<sup>2</sup> (approximately 80-100 mg). Therefore, there are no longer any restrictions on the use of acetaminophen or acetaminophen-containing products in combination with selinexor, EXCEPT on days on selinexor dosing, when acetaminophen must not exceed a total daily dose of 1 gram.

Patients should not take glutathione (GSH)-, S-adenosylmethionine (SAM)-, or N-acetylcysteine (NAC)-containing products during their participation in this study as these products may enhance the metabolism of selinexor. Please see *Appendix 9* for a list of representative products. Patients must report all prescription and non-prescription medicines to their physicians during this study.

*Diet:* There are no dietary restrictions on this study. Patients should maintain adequate caloric and fluid intake.

## 12.5 TREATMENT COMPLIANCE

The investigator or other study staff will supervise study drug treatment given in the clinic and instruct the patient on study medication self-administration.

Patients will be asked to bring their study medication container with them at the each visit and compliance with protocol-defined study drug intake will be checked by pill count.

Compliance to study medication will be recorded by study personnel after discussion with the patient and drug accountability. Compliance to study medication will be assessed by the Investigator or delegate and recorded in source documents. The date will be recorded as per study drug schedule. The Investigator or the designee will account for the number of tablets dispensed against those returned by the patient. Any deviations and missed doses will be recorded in the eCRF and drug accountability logs for verification with the reasons.

The investigator or designee will try to ensure complete compliance with the dosing schedule by providing timely instructions to the patients. In case of non-compliance, the patients will be instructed again.

## 13 ADVERSE EVENTS

An AE is defined as any undesired medical occurrence in a patient or clinical investigation patient receiving a pharmaceutical product regardless of a causal relationship with this treatment. An AE can therefore be any unfavorable sign and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a study drug, whether or not related to the study drug.

Any treatment-emergent abnormal laboratory result, which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the AE page in the eCRF:

1. Accompanied by clinical symptoms
2. Leading to a change in study medication (e.g., dose modification, interruption or permanent discontinuation)
3. Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

It is the responsibility of the investigator to document all AEs that occur during the study. AE information will be elicited by asking the patient a non-leading 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 eCRF.

AEs should be reported for their actual grade and duration.

The term “severe” is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (e.g., ‘severe’ headache). This is not the same as “serious.” Seriousness of AEs is based on the outcome of an AE and usually associated with events that pose a threat to a patient’s life or functioning.

The severity of the AE will be graded according to the CTCAE Grading Scale (see the CTCAE web page at <http://ctep.cancer.gov> for details). For AEs not covered by CTCAE, the severity will be characterized as “mild,” “moderate,” or “severe” according to the following definitions:

- Mild events are usually transient and do not interfere with the patient’s daily activities.
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Severe events interrupt the patient’s usual daily activities.

The investigator will make a judgment regarding the AE’s relationship to study drug, as outlined below in *Table 13.1*.

**Table 13.1 Classification of Adverse Events by Causality**

<b>Not related</b>	The lack of a temporal relationship of the event to study treatment makes a causal relationship not reasonably possible, or by any other drugs, therapeutic interventions or underlying conditions that provide a sufficient explanation
<b>Possibly related</b>	The temporal relationship of the event to study treatment makes a causal relationship reasonably possible, and the event is more likely explained by exposure to the study treatment than by any other drugs, therapeutic interventions or underlying conditions
<b>Related</b>	The temporal relationship of the event to study treatment makes a definitive relationship, and the event is more likely explained by exposure to the study treatment than by any other drugs, therapeutic interventions or underlying conditions

### 13.1 SERIOUS ADVERSE EVENTS, OVERDOSE

A SAE is any untoward medical occurrence that occurs at any dose (including after the ICF is signed and prior to dosing) that:

- Results in death
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- 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 on appropriate medical judgment, they may jeopardize the patient 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-patient 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.

Progression of the malignancy (including fatal outcomes) if documented per IMWG criteria for progression of MM (see *Appendix 3*), should not be reported as an SAE during the study or within the safety reporting period (see below).



Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

### **13.1.1 AE and SAE Follow-up**

All AEs occurring during the study are to be followed up in accordance with good medical practice until they are resolved, stabilized or judged no longer clinically significant or, if a chronic condition, until fully characterized. Any AEs that are considered drug-related (possibly related, related) must be followed until resolution or until stabilization. Any AE of rash should be documented until resolution with photographs.

### **13.1.2 Post-Study Adverse Events and Serious Adverse Events**

All unresolved AEs should be followed by the investigator until the events are resolved, the patient is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the investigator should instruct each patient to report any subsequent event(s) that the patient, or the patient's personal physician, believes might reasonably be related to participation in this study. Prior to the conclusion of the study at the site, the investigator should notify the Safety Associate (see *Section 13.1.5.1*) of any death or AE occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to this study.

For any patient who discontinues from the study, a Survival Follow-Up telephone call (see *Table 1.1* and *Section 9.2*) will be made by study personnel every 30 days to the patient (or the patient's family) to inquire about the patient's multiple myeloma status and well-being.

After study conclusion, the investigator should notify Karyopharm Therapeutics, Inc., or their designee, of any death or AE he or she is aware of occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to this study. Karyopharm Therapeutics, Inc. 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 patient that has participated in this study.

### **13.1.3 Overdose**

An overdose is defined as a deliberate or accidental administration of study medication to a study patient at a dose above that which is assigned to that individual patient according to the study protocol. In the event of drug overdose, the investigator should be notified immediately and the patient observed closely for AEs. The patient should be treated symptomatically as appropriate, and the incident of overdose and related AEs and/or treatment documented in the patient's medical record.

As selinexor is metabolized by GSH conjugation, it is conceivable that hepatic GSH depletion can occur in case of overdose. Therefore, in patients who develop liver function test abnormalities, supportive measures such as SAM 400 mg orally 1-4 times a day, or other drugs that can replace GSH, should be considered.

### **13.1.4 Pregnancies**

Pregnancy *per se* is not considered an AE unless there is cause to believe that the investigational drug may have interfered with the effectiveness of a contraceptive medication.

Each pregnancy in a patient or partner of a patient on selinexor must be reported to the Sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Follow-up and documentation must occur even if the patient withdraws from the study or the study is completed.

The avoidance of fathering a child is suggested for 3 months following the discontinuation of selinexor therapy. No information is currently available regarding the effects of selinexor on fertility, gestation or subsequent child development.

Any pregnancy within 3 months post-study should be reported to the study investigator and the sponsor's designee.

### **13.1.5 Serious Adverse Event Reporting**

#### **13.1.5.1 Reporting Requirements**

Unexpected serious suspected adverse reactions are subject to expedited reporting to regulatory authorities. ALL SAEs must be entered into the eCRF and reported to the Sponsor's designee within 24 hours of first knowledge of the event by study personnel. It is important that the investigator provide his/her assessment of relationship to study drug at the time of the initial report. Entry of an SAE into the eCRF triggers an automatic alert to the Sponsor's designee. Timely notification of an event supersedes the requirement to have all information at the time of the initial report. The following information must be reported on the eCRF SAE report form:

- Protocol number
- Site and/or investigator number
- Patient number
- Demographic data
- Brief description of the event
- Onset date and time
- Resolution date and time, if the event resolved
- Current status, if event not yet resolved
- Any concomitant treatment and medication
- Investigator's assessment of the SAE's relationship to investigational product
- Outcome of the event if available

The Sponsor's designee will contact the site for clarification of data entered into the eCRF or to obtain missing information. In the event of questions regarding SAE reporting, the site may contact:

Safety Associate  
Clinipace Worldwide, Inc.  
safety@clinipace.com

The SAE report will be distributed to the Karyopharm safety distribution list.

Karyopharm, or their designee, is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to FDA according to 21 CFR 312.32 and applicable regulatory guidance documents and other regulatory agencies according to country-specific guidelines. 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) or Independent Ethics committee (IEC).

Reporting of SAEs by the investigator to the IRB or IEC will be done in accordance with the standard operation procedures and policies of the IRB/IEC. Adequate documentation must be maintained showing that the IRB/IEC was properly notified.

## 14 STATISTICAL METHODS

### 14.1 GENERAL CONSIDERATIONS

#### 14.1.1 Statistical and Analytical Plans

This is a Phase 2b, single-arm, open-label, multicenter study of selinexor (80 mg) with low-dose (20 mg) dexamethasone given orally to patients with heavily pretreated, quad-refractory MM.

Hypothesis testing will be used for the primary efficacy endpoint data, in order to evaluate if selinexor plus low-dose dexamethasone provides statistically significant improvement in efficacy over a minimally acceptable level of 15% ORR. No formal hypothesis-testing will be used for other study data, such as demographics and safety data.

Tabulations will be produced for appropriate disposition, demographic, baseline, efficacy and safety parameters. For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented, as well as two-sided 95% confidence intervals (CI), unless otherwise stated. For continuous variables, the number of patients, mean, median, standard deviation (SD), minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier (KM) methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals, as well as percentage of censored observations.

#### 14.1.2 Determination of Sample Size

The sample size study was chosen to address the primary study objective: to evaluate the clinical effect of selinexor plus dexamethasone by reference to a minimal threshold level for ORR, set to 0.15 (15%). The statistical test associated with the comparison to the threshold will maintain a Type I error rate of 0.025, one-sided. A sample size of approximately 80 patients will provide 90% power for a one-sided test at  $\alpha=0.025$  to detect an ORR of  $\geq 0.30$  against the threshold ORR of 0.15.

#### 14.1.3 Disposition of Patients

A tabulation of patient disposition will be presented, including the number in each analysis population, the number with non-evaluable disease according to the IMWG criteria, the number censored at each of the PFS and OS analyses, the number lost to follow-up, the number that withdrew prior to completing the study, and reason(s) for withdrawal.

#### 14.1.4 Blinding and Randomization

This is an open-label, single-arm study, therefore blinding and randomization are not applicable.

#### 14.1.5 Dose Adjustment

The dose level for an individual patient may be escalated, based on efficacy considerations, after a minimum of 2 cycles of study therapy. Reasons for dose escalation can include, for example, a response of stable disease or partial response with acceptable safety. Dose reduction can take place, based on the guidelines in *Section 12.1.6*. Additional exploratory

analyses may be performed that investigate the impact of dose changes, should there be a sufficient number of dose adjustments.

## **14.2 ANALYSIS DATASETS**

### **14.2.1 Population to be Analyzed**

#### **14.2.1.1 Modified Intent-to-Treat Population**

The Modified Intent-to-Treat (mITT) population will consist of all patients who received at least one dose of study treatment. This population will include patients who have discontinued therapy due to toxicity or disease progression and patients who have died from any cause, including those related to study drug or disease. This population will be used for primary analyses of efficacy.

#### **14.2.1.2 Per Protocol Population**

The per-protocol (PP) population will consist of all patients who have received at least one cycle (i.e., Weeks 1-3) of study drug treatment, are compliant with study assessments, have received at least 80% of their prescribed study medication, and have no major protocol violations that would compromise the assessment of efficacy. Major violations will be determined independently of knowledge of response to therapy, prior to database lock and study analysis. This population will be used for supportive inferences concerning efficacy, however, if there are major differences between the results in this population and those obtained in the mITT population, this will be taken into consideration in the assessment of efficacy.

#### **14.2.1.3 Safety Population**

The safety population will consist of all patients who have received at least one dose of study treatment and have any post-baseline safety information.

## **14.3 DATA ANALYSIS AND PRESENTATION**

Summary tabulations for the overall population will be provided for disposition as noted above, and for demographic, baseline, efficacy and safety data as noted in the following sections. All data collected on the eCRF will be provided in by-patient data listings.

### **14.3.1 Demographic Characteristics**

Demographic characteristics will be summarized for the overall population and will include gender, race, ethnicity (Hispanic origin), and age at time of consent. For gender, race, and Hispanic origin, the summary statistics will be the number and percentage of patients within each category. The categories for race will be those recorded in the database. For age at time of consent, the mean, median, minimum, maximum, and standard deviation will be provided for each group and the total sample.

### **14.3.2 Baseline Characteristics and Medical History**

Baseline characteristics include: performance status, duration from initial diagnosis, response to previous therapy, types of prior therapy, and height/weight. Baseline data will be tabulated using summary statistics; no formal hypothesis testing will be performed.

Medical history and physical examination results at baseline will be tabulated.

### **14.3.3 Primary Endpoint**

The primary statistical analysis of efficacy will be performed on ORR (achievement of CR or PR) for the overall mITT population, with supportive data provided by duration of response; it is anticipated that DOR may be on the order of 5-7 months following initial documentation of response. (DOR is defined as the duration of time measured from when response criteria were first met until the first date of recurrence or PD or death.) For the primary analysis of superiority to the minimal threshold ORR, analysis will be performed using a two-sided 95% confidence interval, calculated for the rate of ORR, and statistical significance will be declared if the lower bound of this interval is greater than 20%.

Duration of response will be described using the stratified Kaplan-Meier (KM) method, with strata defined by ISS stage III versus stage I or II, including an estimate of the median, as well as the 25<sup>th</sup> and 75<sup>th</sup> percentiles, along with two-sided 95% confidence intervals.

### **14.3.4 Secondary Endpoints**

Key secondary endpoints, including CBR, DCR, PFS, QoL and OS will be statistically evaluated using appropriate confidence intervals following statistical significance of the primary endpoint at each dose level of study treatment. Statistical tests will be performed at the one-sided, 0.025 level. CBR will be assessed for statistical significance only if the primary endpoint ORR is statistically significant. Significance of CBR will be established if the lower bound of the two-sided 95% CI on CBR is greater than a minimal threshold value of 35%. Subsequent to a significant result for CBR, DCR will be analyzed in a similar fashion. PFS will be assessed following a significant result for DCR, using KM methods, with descriptive statistical significance declared if the lower bound of the two-sided 95% CI exceeds 6 months. QoL will be assessed using the Functional Assessment of Cancer Therapy-Multiple Myeloma (FACT-MM), with a statistical test for significance of the change from baseline in the Trial Outcome Index; see below for the details of this analysis. OS will be assessed by descriptive statistics, based on the same KM approach as used for PFS.

Quality of life (QoL) will be assessed using the FACT-MM. This instrument combines the General version of the FACT (FACT-G) with a MM-specific subscale (14 items). The subscales for the FACT-G are Physical Well-Being (7 items), Social/Family Well-Being (7 items), Emotional Well-Being (6 items), and Functional Well-Being (7 items). The trial outcomes index (TOI; total of 41 items) will be the primary measurement of interest, comprised of the Physical and Functional subscales plus the MM-specific subscale. Each item is rated on a 5-point Likert scale, ranging from 0 (=“Not at all”) to 4 (=“Very much”), therefore the TOI has a score ranging from 0 to 120. The QoL assessment will be performed at Baseline (prior to first dose of study treatment), Day 1 of each cycle on or after the second, and at the Final visit. The primary endpoint analysis will take place based on changes in the total TOI score from Baseline using paired T-tests. A secondary analysis of QoL will be performed in a similar manner using the total of all subscales. All 5 individual subscale total scores will be summarized over time using descriptive statistics.

Duration of response (DOR) will be calculated, for patients achieving response (ORR), as the duration from the date when first evidence of objective disease response was achieved based on IMWG criteria, until the first date of recurrence, PD, or death. The start of DCR will be based on the date of first receipt of treatment. The duration of response for each respective type of response will be regarded as descriptive adjuncts to the analyses of response rates. Analysis of duration of each response type will be performed using KM methods.

#### **14.3.5 Additional Secondary and Exploratory Endpoints**

Supportive efficacy endpoint analyses will be performed using descriptive statistics, since such analyses are expected to be either supportive of the key efficacy endpoint results or hypothesis-generating and are not intended in this study to provide primary or confirmatory evidence of efficacy.

The comparison of the Sel-Dex TTP in the current study to TTP on prior MM therapies will be performed as an additional secondary analysis, supportive to the primary PFS analysis. This analysis may be performed with both categorical and time to event statistical methods. For categorical analysis, patients will be classified as having a TTP that is either shorter, longer or the same as their prior therapy TTP (where “same” will be defined as  $\pm 10\%$  of the prior TTP). For the time to event analysis, the difference between the current study TTP and prior therapy TTP will be analyzed. Note that TTP for the current study may represent censored results, therefore, to minimize the impact of censoring, this analysis may require maturation of the TTP data beyond the required time at which the number of events for the primary PFS analysis have occurred.

Several subgroup comparisons of interest may be evaluated. These subgroup analyses would be descriptive, rather than confirmatory, in nature, since the study has not been powered to determine specific differences amongst the subgroups relative to the efficacy of study treatment. Two specific subgroup analyses will be conducted. The first sub-group analysis will be ORR in quad-refractory vs. penta-refractory patients. The second subgroup analysis will be based on the use of the ISS stage. Summary statistics will be presented for each of two staging levels (III vs. I or II).

Analyses of ORR, DOR, PFS, and OS will be conducted in patient with FLC myeloma and in patients undergoing dose increase during the study

Additional exploratory subgroup analyses may be performed, to evaluate response as related to:

- Cytogenetic and fluorescent in situ hybridization (FISH) prognostic markers including p53 abnormalities and chromosomal aberrations (e.g., del 17p, t(4;14), t(14;16), del 13) and other MM cytogenetic classifications
- Gene expression and plasma protein levels
- Time since initial diagnosis of active myeloma
- Lytic lesions as measured by skeletal survey

### **14.3.6 Pharmacokinetic and Pharmacodynamic Data**

Plasma samples will be analyzed via a validated high performance liquid chromatography/tandem mass spectrometry (HPLC/MS-MS) method for plasma selinexor concentration. Selinexor concentration data will be analyzed in a non-linear mixed effects population PK model with potential covariates including, but not limited to: age, body weight, gender, disease state, baseline hepatic or renal function, concomitant medications, and treatment. Measurements of selected plasma protein levels may be added as covariates in the PK analysis in order to investigate potential PK/PDn relationships. Details of the population PK analysis, including software, post-processing and statistical analysis, will be outlined in a separate PK/PDn Data Analysis Plan, to be completed prior to database lock. Results of these detailed PK and PK/PDn analyses may be presented in a separate report from, or appendix to, the primary clinical study report for this trial.

Interim analyses may be conducted on draft plasma selinexor concentration data throughout the study. Summary statistics, including mean, median, standard deviation, coefficient of variation and group size may be compiled and reported during the study. Interim analysis of key selinexor PK parameters and key biomarker analyses may be performed in order to provide a pharmacokinetic-pharmacodynamic assessment throughout the study.

### **14.3.7 Safety Data**

Safety analyses will be performed on the Safety Population, including all patients who received at least one dose of study treatment. The original dose level for each patient will be used for safety analysis; no separate categories for dose escalation or reduction will be conducted in the primary analysis of safety. Additional exploratory evaluation of the impact of dose escalation or reduction on safety may be performed.

#### **14.3.7.1 Adverse Events**

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and displayed in tables and listings using MedDRA system organ class (SOC) and Preferred Term (PT).

Analyses of AEs will be performed for those events that are considered treatment emergent, where treatment-emergent is defined as any AE with onset, or worsening of a pre-existing condition, on or after the first dose of randomized treatment through 30 days following the last dose of randomized treatment, or any event considered drug-related by the investigator through the end of the study. AEs with partial dates will be assessed using the available date information to determine if treatment-emergent; AEs with completely missing dates will be assumed to be treatment-emergent. No formal hypothesis-testing of AE incidence rates will be performed.

AEs will be summarized by patient incidence rates, therefore, in any tabulation, a patient contributes only once to the count for a given AE (preferred term). The number and percentage of patients with any treatment-emergent adverse event (TEAE) will be summarized for each treatment group, classified by SOC and preferred term. The number and percentage of patients with TEAEs assessed by the investigator as at least possibly related to treatment will also be tabulated. The number and percentage of patients with any Grade  $\geq 3$  TEAE will be tabulated in the same manner.



The investigator will judge the causal relationship between the occurrence of an AE and the study drug as not related, possibly related, or related. In the event a patient repeatedly experiences episodes of the same AE, then the event with the highest severity and/or strongest causal relationship to treatment will be used for purposes of tabulations.

All reported SAEs will be tabulated.

All AEs (treatment-emergent and post-treatment) will be listed in by-patient data listings, classified by treatment, patient and day on study. In addition, separate by-patient listings will be provided for the following: deaths; SAEs; and AEs leading to withdrawal.

#### **14.3.7.2 Laboratory Data**

Clinical laboratory values will be expressed using conventional units. For each treatment arm, the actual value and change from baseline (Day 1, prior to the first administration of study drug) to each on study evaluation will be summarized for each clinical laboratory parameter, including hematology, clinical chemistry, coagulation and urinalysis. In the event of repeat values, the last non-missing value per study day/time will be used. In the event that Day 1 data are unavailable for a given patient/parameter, the Screening value will substitute as the baseline value.

Severity of select clinical lab measures will be determined using CTCAE 4.03 criteria (e.g., those measures that have a corresponding CTCAE grade classification). Labs with CTCAE Grades  $\geq 3$  will be presented in a data listing. Shift tables that present changes from Baseline to worst on-study and Baseline to last on-study values relative to CTCAE classification ranges will be produced.

#### **14.3.7.3 Vital Signs and Physical Examinations**

The actual value and change from baseline (Day 1) to each on-study evaluation will be summarized for vital signs. By-patient listings of vital sign measurements will be presented in data listings.

Physical examination results at screening, and physical examination results changes during the study, will be summarized. All physical examination findings will be presented in by-patient data listings.

#### **14.3.7.4 Concomitant Medications**

The use of concomitant medications will be included in by-patient data listings.

#### **14.3.8 Procedures for Handling Missing Data**

No imputation of missing efficacy data is planned. Patients who have no response recorded post-baseline will be reported as failures in the analysis of ORR, CBR and DCR. For time-to-event analyses, patients who have no efficacy evaluations will be considered as censored at time 0. For PFS, patients who have not had disease progression or are non-evaluable at the final analysis will be censored on the date they were last evaluated for response assessment. For OS, patients will be followed until either lost to follow-up, withdrawal, or death. Patients will be censored on the date they were last known to be alive, regardless of disease status.

For AEs, missing dates will not be imputed; however if partial dates are available, they will be used to assess if the AE occurred during the treatment period. Missing severities of AEs

will not be imputed and will be considered missing in any tabulations of AE severity. If an AE is missing a response to the question regarding relationship to treatment, the event will be considered to be related.

#### **14.4 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS**

All deviations from the original statistical analysis plan will be documented and provided in the final clinical study report.

## **15 REGULATORY, ETHICAL AND LEGAL OBLIGATIONS**

### **15.1 REGULATORY AND ETHICAL COMPLIANCE**

This clinical study was designed, and shall be implemented and reported in accordance with, the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), Division 5 of the Health Canada Food and Drug Regulations - Drugs For Clinical Trials Involving Human Subjects, and with the ethical principles laid down in the Declaration of Helsinki.

### **15.2 INSTITUTIONAL REVIEW BOARDS/ETHICS COMMITTEES**

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Karyopharm, Quality Assurance representatives, designated agents of Karyopharm, IRBs/IECs/REBs and regulatory authorities as required.

### **15.3 REGULATORY AUTHORITY APPROVAL**

Before implementing this study, the protocol must be approved by the relevant, competent regulatory authority.

### **15.4 PROTOCOL ADHERENCE**

Investigators ascertain they will apply due diligence to avoid protocol deviations. All significant protocol deviations will be recorded and reported in the CSR.

### **15.5 AMENDMENTS TO THE PROTOCOL**

Any change or addition to the protocol can only be made in a written protocol amendment that must be provided by Karyopharm, and approved by Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Karyopharm should be notified of this action and the IRB/IEC/REB at the study site should be informed according to local regulations (e.g., the UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

### **15.6 INFORMED CONSENT**

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent

should be documented in the patient source documents. The date when a patient's Informed Consent was actually obtained will be captured in their eCRFs.

Karyopharm will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Karyopharm or their designee must agree to any investigator suggested changes to this ICF before their submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Karyopharm or designee after IRB/IEC/REB approval. Additionally, consent will be requested to obtain/retain a blood sample for future analysis as warranted by our rapidly-advancing understanding in this field. Each patient's informed consent document will reflect that samples collected may be used for pharmacogenomic investigations.

## **15.7 PATIENT CONFIDENTIALITY AND DISCLOSURE**

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Karyopharm or their designees. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

## **15.8 COLLECTION, AUDITING STUDY DOCUMENTATION, AND DATA STORAGE**

### **15.8.1 Study Documentation, Record Keeping and Retention of Documents**

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. Each site will permit authorized representatives of the sponsor and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study eCRF is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRFs, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. For electronic CRFs an audit trail will be maintained by the system.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

### **15.8.2 Auditing Procedure**

In addition to the routine monitoring procedures, the Sponsor or the regulatory authority may conduct an audit or an inspection (during the study or after its completion) to evaluate compliance with the protocol and the principles of GCP.

The investigator agrees that representatives of the Sponsor and Regulatory Authorities will have direct access, both during and after the course of this study, to audit and review all study-relevant medical records.

In the event that a major compliance or regulatory issues arises, the Sponsor may conduct an audit without prior warning.

## **15.9 DISCLOSURE OF INFORMATION**

All information provided to the investigator by Karyopharm, or their designee, will be kept strictly confidential. No disclosure shall be made except in accordance with a right of publication granted to the investigator in the Clinical Trial Agreement.

No information about this study or its progress will be provided to anyone not involved in the study other than to Karyopharm, or its authorized representatives, or in confidence to the IRB, or similar committee, except if required by law.

## **15.10 DISCONTINUATION OF THE STUDY**

It is agreed that, for reasonable cause, either the investigator or Karyopharm, may terminate the investigator's participation in this study after submission of a written notice. Karyopharm may terminate the study at any time upon immediate notice for any reason including the Sponsor's belief that discontinuation of the study is necessary for the safety of patients.

## **15.11 REPORTING AND PUBLICATION OF STUDY DOCUMENTATION**

Karyopharm assures that the key design elements of this protocol will be posted in a publicly accessible database such as [www.clinicaltrials.gov](http://www.clinicaltrials.gov). In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

## 16 REFERENCES

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## **17 APPENDICES**

## **APPENDIX 1      EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS CRITERIA**

(Reference: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655)

<b>ECOG Performance Status Scale</b>	
<b>Grade</b>	<b>Descriptions</b>
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. 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	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

## APPENDIX 2      INTERNATIONAL STAGING SYSTEM FOR MULTIPLE MYELOMA

(Reference: Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. *J Clin Oncol*. 2005;23:3412-3420)

Stage	Characteristics
Stage I	$\beta_2$ -microglobulin <3.5 mg/L, albumin $\geq$ 3.5 g/dL
Stage II	$\beta_2$ -microglobulin <3.5 mg/L and albumin <3.5 g/dL, or $\beta_2$ -microglobulin 3.5-5.5 mg/L irrespective of the serum albumin
Stage III	$\beta_2$ -microglobulin $\geq$ 5.5 mg/L

### APPENDIX 3 INTERNATIONAL MYELOMA WORKING GROUP RESPONSE CRITERIA, MYELOMA

(Reference: Modified from: Kyle RA and Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. *Leukemia*. 2009;23:3-9.)

Response subcategory	Response criteria
Complete response (CR) <sup>a</sup>	Negative immunofixation of serum and urine and disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow
Stringent complete response (sCR)	CR as defined above plus: Normal FLC ratio and <span style="float: right;">absent</span> marrow by immunohistochemistry or immunofluorescence
Very good partial response (VGPR) <sup>a</sup>	Serum and urine M-component detectable by immunofixation but not on electrophoresis or $\geq 90\%$ or greater reduction in serum M-component plus urine M-component < 100 mg per 24 h
Partial response (PR)	$\geq 50\%$ reduction of serum M protein and reduction in 24-h urinary M protein by $\geq 90\%$ or to < 200 mg per 24 h If the serum and urine M protein are unmeasurable, a $\geq 50\%$ decrease in the difference between involved and uninvolved FLC levels is required in place of the M protein criteria If serum and urine M protein are unmeasurable, and serum free light assay is also unmeasurable, $\geq 50\%$ reduction in bone marrow plasma cells is required in place of M protein, provided baseline percentage was $\geq 30\%$ In addition to the above criteria, if present at baseline, $\geq 50\%$ reduction in the size of soft tissue plasmacytomas is also required
Minor response (MR) in patients with relapsed refractory myeloma	$\geq 25\%$ but < 49% reduction of serum M protein and reduction in 24 h urine M protein by 50–89%, which still exceeds 200 mg per 24 h In addition to the above criteria, if present at baseline, 25–49% reduction in the size of soft tissue plasmacytomas is also required No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR or progressive disease
Progressive disease (PD) <sup>a</sup>	Increase of 25% from lowest response value in any one or more of the following:

	<p>Serum M-component (absolute increase must be <math>\geq 0.5</math> g/100 ml)<sup>b</sup> and/or Urine M-component (absolute increase must be <math>\geq 200</math> mg per 24 h) and/or</p> <p>Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved</p> <p>FLC levels (absolute increase must be <math>&gt; 10</math> mg/l). Bone marrow plasma cell percentage (absolute % must be <math>\geq 10\%</math>)</p> <p>Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas</p> <p>Development of hypercalcemia (corrected serum calcium <math>&gt; 11.5</math> mg/100 ml) that can be attributed solely to the plasma cell proliferative disorder</p>
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<sup>a</sup>Note clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a  $> 90\%$  decrease in the difference between involved and uninvolved FLC levels.

All response categories (CR, sCR, VGPR and PR) require two consecutive assessments made at any time before the institution of any new therapy; complete, PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed.

<sup>b</sup>For progressive disease, serum M-component increases of  $\geq 1$  gm/100 ml are sufficient to define relapse if starting M-component is  $\geq 5$  gm/100 ml.

## APPENDIX 4 QUALITY OF LIFE (FACT-MM) QUESTIONNAIRE

(Reference: [www.FACIT.org](http://www.FACIT.org))

Below is a list of statements that other people with your illness have said are important.  
**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

### PHYSICAL WELL-BEING

		Not at all	A little bit	Some- what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

### SOCIAL/FAMILY WELL-BEING

		Not at all	A little bit	Some- what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4

Q1	<b>REGARDLESS OF YOUR CURRENT LEVEL OF SEXUAL ACTIVITY, PLEASE ANSWER THE FOLLOWING QUESTION. IF YOU PREFER NOT TO ANSWER IT, PLEASE CHECK THIS BOX</b>					
GS7	<input type="checkbox"/>	<b>AND GO TO THE NEXT SECTION.</b>				
	I am satisfied with my sex life	0	1	2	3	4

**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

**EMOTIONAL WELL-BEING**

		Not at all	A little bit	Some- what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

**FUNCTIONAL WELL-BEING**

		Not at all	A little bit	Some- what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4



**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

ADDITIONAL CONCERNS		Not at all	A little bit	Some- what	Quite a bit	Very much
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
HI 12	I feel weak all over	0	1	2	3	4
BMT 6	I get tired easily	0	1	2	3	4
HI8	I have trouble concentrating	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU3	I feel discouraged about my illness	0	1	2	3	4
LEU4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
BP1	I have bone pain	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
MM1	I have trouble walking because of pain	0	1	2	3	4
HI7	I feel fatigued	0	1	2	3	4
ES 10	I have gained weight	0	1	2	3	4

## **APPENDIX 5      SELINEXOR FORMULATION AND ADMINISTRATION**

### **Description of Selinexor (KPT-330)**

Selinexor is a Selective Inhibitor of Nuclear Export (SINE) compound. Selinexor specifically blocks nuclear export by binding to the nuclear export protein XPO1.

*The chemical name is:* (Z)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)-N'-(pyrazin-2-yl)acrylohydrazide

*The molecular formula is:* C<sub>17</sub>H<sub>11</sub>F<sub>6</sub>N<sub>7</sub>O.

*The molecular weight is:* 443.31

### **Form**

Selinexor will be supplied and administered as either (a) 20 mg, or (b) 10 mg and 25 mg, coated, immediate-release tablets.

### **Storage and Stability**

Tablets of selinexor drug product will be packaged either in (a) polyvinyl chloride/polyethylene/polychlorotrifluoroethylene (PVC/PE/PCTFE) film blisters with a paperbacked foil and a secondary wallet for labeling and childproofing, or (b) multi-dose containers of 50 tablets. Selinexor should be stored in a locked and secured area with access restricted to the site staff pharmacist or designee(s), with temperature at or below 30°C (86°F). Room temperature storage is recommended, refrigerated is suitable. Tablets should not be stored frozen.

Selinexor tablets (all strengths) are currently in on-going stability studies. The expiry will be based on concurrent stability studies and extended during the course of the study as further stability data becomes available.

### **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

### **Availability**

Selinexor is an investigational agent and will be supplied free-of-charge from Karyopharm Therapeutics, Inc.

### **Preparation**

No special preparation required.

NOTE: Tablets of selinexor should not be crushed because of increased risk of dermatologic toxicity if powder comes in contact with skin.

### **Administration**

Selinexor will be provided as tablets for oral administration. Selinexor is to be taken within 30 minutes of solid food consumption together with at least 120 mL (4 ounces) of fluids (water, milk, etc.).

Selinexor dosing will be initiated at an oral dose of 80 mg twice weekly (Monday and Wednesday or Tuesday and Thursday or Wednesday and Friday). Selinexor will be taken twice weekly during Weeks 1, 2, and 3 of each four-week cycle.

### **Ordering**

Drug order forms with all needed contact information will be provided at the start of the trial, along with recommended initial and resupply stock orders. Orders submitted via e-mail will generally be filled within 5 business days of receipt.

### **Accountability**

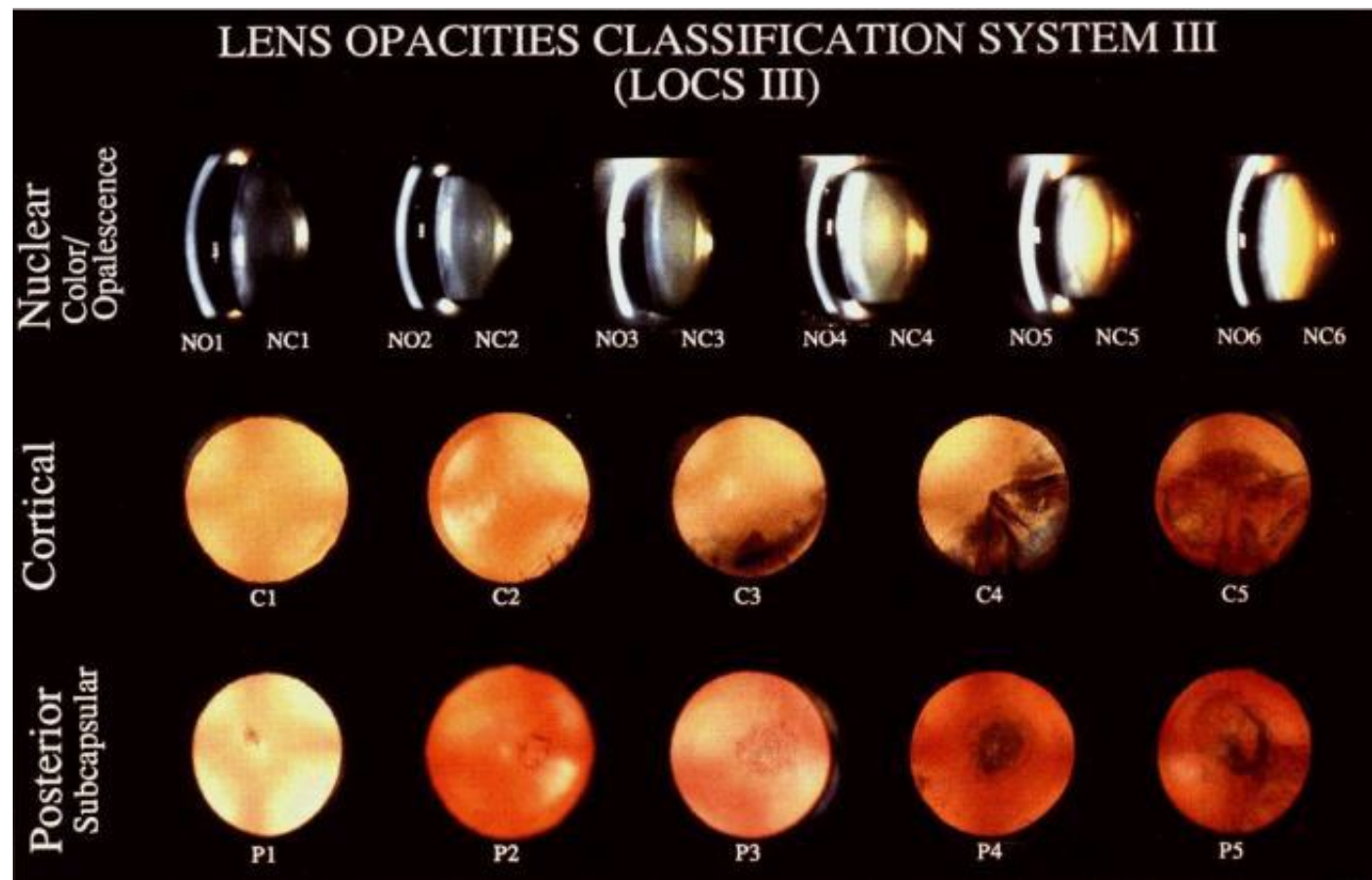
The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (see the Cancer Therapy Evaluation Program [CTEP] website at <http://ctep.cancer.gov/protocolDevelopment> for the “Policy and Guidelines for Accountability and Storage of Investigational Agents” or to obtain a copy of the drug accountability form).

### **Destruction and Return**

At the end of the study, unused supplies of selinexor should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

## APPENDIX 6 LENS OPACITIES CLASSIFICATION SYSTEM III (LOCS III)

If a cataract is seen during the slit lamp examination to document lens clarity, the cataract will be graded according to the LOCS III.




## Ophthalmological Exam Assessments

Best Corrected Visual Acuity (BCVA):			
	Normal	Abnormal	Description
Adnexa			
Lids			
Lashes			
Conjunctiva			
Cornea			
Ant. Chamber			
Iris			
Lens <sup>1</sup>			
Intraocular pressure			
Fundus			
Vitreous			
Optic Disc <sup>2</sup>			
Macula			
Retina			

<sup>1</sup>Does lens show cataract change? Follow grading system in description

<sup>2</sup>Cup/disc ratio and any abnormalities, if observed

## APPENDIX 7 NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY: ANTIEMESIS



National  
Comprehensive  
Cancer  
Network®

**NCCN Guidelines Version 2.2014**  
**Antiemesis**

[NCCN Guidelines Index](#)  
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**HIGH EMETIC RISK INTRAVENOUS CHEMOTHERAPY - ACUTE AND DELAYED EMESIS PREVENTION<sup>a,b,c</sup>**  
Start before chemotherapy<sup>c,d</sup>

Neurokinin 1 antagonist containing regimen consisting of the following:

- **Serotonin (5-HT<sub>3</sub>) antagonist (Choose one):<sup>e,f</sup>**
  - ▶ Dolasetron 100 mg PO<sup>g</sup>
  - ▶ Granisetron 2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (max 1 mg) IV day 1<sup>g</sup> or transdermal patch as 3.1 mg/24 h patch (containing 34.3 mg granisetron total dose) applied approximately 24-48 h prior to first dose of chemotherapy; maximum duration of patch is 7 days
  - ▶ Ondansetron 16-24 mg PO or 8-16 mg IV day 1<sup>g,h</sup>
  - ▶ Palonosetron 0.25 mg IV day 1 (preferred)<sup>i</sup>
- AND
- **Steroid (Choose one):<sup>j</sup>**
  - ▶ Dexamethasone 12 mg PO or IV day 1, 8 mg PO daily days 2-4 (with aprepitant 125 mg)
  - ▶ Dexamethasone 12 mg PO or IV day 1, 8 mg PO day 2, then 8 mg PO BID days 3 and 4 (with fosaprepitant 150 mg IV day 1)
- AND
- **Neurokinin 1 antagonist (Choose one):**
  - ▶ Aprepitant 125 mg PO day 1, 80 mg PO daily days 2-3
  - ▶ Fosaprepitant 150 mg IV day 1 only
- ± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 hours or every 6 hours days 1-4
- ± H<sub>2</sub> blocker or proton pump inhibitor

→ [See Breakthrough Treatment \(AE-6\)](#)

category 1 for combined regimens<sup>c</sup>

OR

- **Olanzapine-containing regimen<sup>k</sup>**
  - ▶ Olanzapine 10 mg PO days 1-4
  - ▶ Palonosetron 0.25 mg IV day 1
  - ▶ Dexamethasone 20 mg IV day 1
- ± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 hours or every 6 hours days 1-4
- ± H<sub>2</sub> blocker or proton pump inhibitor

→ [See Breakthrough Treatment \(AE-6\)](#)

<sup>a</sup>Data for post-displatin (>50 mg/m<sup>2</sup>) emesis prevention are category 1; others are category 2A.

<sup>b</sup>See [Emetogenic Potential of Intravenous Antineoplastic Agents \(AE-7\)](#).

<sup>c</sup>Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors.

<sup>d</sup>See [Principles of Managing Multiday Emetogenic Chemotherapy Regimens \(AE-8\)](#).

<sup>e</sup>Order of listed antiemetics is alphabetical.

<sup>f</sup>Serotonin (5-HT<sub>3</sub>) antagonists may increase the risk of developing prolongation of the QT interval of the electrocardiogram. [See Discussion](#).

<sup>g</sup>Some NCCN Member Institutions use a 5-HT<sub>3</sub> antagonist on days 2-3.

<sup>h</sup>The FDA recommends a maximum of 16 mg for a single dose of IV ondansetron.

<sup>i</sup>Data with palonosetron are based on randomized studies in combination with steroids only.

<sup>j</sup>Use of steroids is contraindicated with drugs such as interleukin-2 (ie, IL-2, aldesleukin) and interferon.


<sup>k</sup>Navari RM, Gray SE, Kerr AC. Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. J Support Oncol 2011;9:188-195.

**Note:** All recommendations are category 2A unless otherwise indicated.  
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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AE-2

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**MODERATE EMETIC RISK INTRAVENOUS CHEMOTHERAPY - EMESIS PREVENTION<sup>b,c,l</sup>**

**DAY 1**

Start before chemotherapy<sup>c,d</sup>  
5HT3 antagonist + steroid ± NK1 antagonist regimen consisting of the following:

- **Serotonin (5-HT3) antagonist (category 1) (Choose one):<sup>e,f</sup>**
  - ▶ Dolasetron 100 mg PO
  - ▶ Granisetron 2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (max 1 mg) IV day 1 or transdermal patch as 3.1 mg/24 h patch (containing 34.3 mg granisetron total dose) applied approximately 24 to 48 h prior to first dose of chemotherapy; maximum duration of patch is 7 days
  - ▶ Ondansetron 16-24 mg PO or 8-16 mg IV<sup>h</sup>
  - ▶ Palonosetron 0.25 mg IV (preferred)<sup>l</sup>

**AND**

- **Steroid:<sup>j</sup>**
  - ▶ Dexamethasone 12 mg PO or IV

**WITH/WITHOUT**

- Neurokinin 1 antagonist (Choose one; for selected patients, where appropriate)<sup>l</sup>
  - ▶ Aprepitant 125 mg PO
  - ▶ Fosaprepitant 150 mg IV
- ± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h PRN
- ± H2 blocker or proton pump inhibitor

**OR**

- Olanzapine-containing regimen<sup>k</sup>
  - ▶ Olanzapine 10 mg PO
  - ▶ Palonosetron 0.25 mg IV
  - ▶ Dexamethasone 20 mg IV
- ± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h PRN
- ± H2 blocker or proton pump inhibitor

**DAYS 2 and 3**

- **Serotonin (5-HT3) antagonist monotherapy (unless palonosetron used on Day 1) (Choose one):<sup>e,f</sup>**
  - ▶ Dolasetron 100 mg PO daily
  - ▶ Granisetron 1-2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (maximum 1 mg) IV
  - ▶ Ondansetron 8 mg PO BID or 16 mg PO daily or 8-16 mg IV<sup>h</sup>
- OR**
- **Steroid monotherapy:<sup>j</sup>**
  - ▶ Dexamethasone 8 mg PO or IV daily
- OR**
- Neurokinin 1 antagonist ± steroid: (if NK-1 antagonist used on day 1)<sup>m</sup>
  - ▶ Aprepitant used day 1: Aprepitant 80 mg PO ± dexamethasone 8 mg PO or IV daily
  - ▶ Fosaprepitant used day 1: ± dexamethasone 8 mg PO or IV daily
- ± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h PRN
- ± H2 blocker or proton pump inhibitor

**OR**

- Olanzapine 10 mg PO days 2-4 (if given day 1)<sup>k</sup>
- ± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h PRN
- ± H2 blocker or proton pump inhibitor

→

→

[See Breakthrough Treatment \(AE-6\)](#)

[See Breakthrough Treatment \(AE-6\)](#)

<sup>b</sup>See [Emetogenic Potential of Intravenous Antineoplastic Agents \(AE-7\)](#).

<sup>c</sup>Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors.

<sup>d</sup>See [Principles of Managing Multiday Emetogenic Chemotherapy Regimens \(AE-A\)](#).

<sup>e</sup>Order of listed antiemetics is alphabetical.

<sup>f</sup>Serotonin (5-HT3) antagonist may increase the risk of developing prolongation of the QT interval of the electrocardiogram. [See Discussion](#).

<sup>h</sup>The FDA recommends a maximum of 16 mg for a single dose of IV ondansetron.

<sup>l</sup>Data with palonosetron are based on randomized studies with steroids only.

<sup>j</sup>Use of steroids is contraindicated with drugs such as interleukin-2 (ie, IL-2, aldesleukin) and interferon.

<sup>k</sup>Navan RM, Gray SE, Kerr AC. Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. *J Support Oncol* 2011;9:188-195.


<sup>l</sup>Data for post-carboplatin ≥300 mg/m<sup>2</sup>, cyclophosphamide ≥800-1000 mg/m<sup>2</sup>, and doxorubicin ≥50 mg/m<sup>2</sup> emesis prevention are category 1.

<sup>m</sup>As per high emetic risk prevention, aprepitant or fosaprepitant should be added (to dexamethasone and a 5-HT3 antagonist regimen) for select patients receiving other chemotherapies of moderate emetic risk (eg, carboplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, methotrexate) ([See AE-2](#)).

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**AE-3**

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BREAKTHROUGH TREATMENT FOR CHEMOTHERAPY-INDUCED NAUSEA/VOMITING <sup>d,r</sup>	RESPONSE TO BREAKTHROUGH ANTIEMETIC TREATMENT	SUBSEQUENT CYCLES
<p><b>Any nausea/vomiting</b></p> <p>The general principle of breakthrough treatment is to add one agent from a different drug class to the current regimen.<sup>e</sup></p> <ul style="list-style-type: none"> <li>• <b>Atypical antipsychotic:</b> <ul style="list-style-type: none"> <li>▶ Olanzapine 10 mg PO daily for 3 days<sup>s</sup></li> </ul> </li> <li>• <b>Benzodiazepine:</b> <ul style="list-style-type: none"> <li>▶ Lorazepam 0.5-2 mg PO or IV either every 4 or every 6 h</li> </ul> </li> <li>• <b>Cannabinoid:</b> <ul style="list-style-type: none"> <li>▶ Dronabinol 5-10 mg PO either every 3 or every 6 h</li> <li>▶ Nabilone 1-2 mg PO BID</li> </ul> </li> <li>• <b>Other:</b> <ul style="list-style-type: none"> <li>▶ Haloperidol 0.5-2 mg PO or IV every 4-6 h<sup>n</sup></li> <li>▶ Metoclopramide 10-40 mg PO or IV either every 4 or every 6 h<sup>n</sup></li> <li>▶ Scopolamine transdermal patch 1 patch every 72 h</li> </ul> </li> <li>• <b>Phenothiazine:</b> <ul style="list-style-type: none"> <li>▶ Prochlorperazine 25 mg supp pr every 12 h or 10 mg PO or IV every 6 h<sup>n</sup></li> <li>▶ Promethazine 12.5-25 mg PO or IV central line only every 4 h<sup>n</sup></li> </ul> </li> <li>• <b>Serotonin 5-HT<sub>3</sub> antagonists:<sup>f</sup></b> <ul style="list-style-type: none"> <li>▶ Dolasetron 100 mg PO daily</li> <li>▶ Granisetron 1-2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (maximum 1 mg) IV</li> <li>▶ Ondansetron 16 mg PO or IV daily</li> </ul> </li> <li>• <b>Steroid:</b> <ul style="list-style-type: none"> <li>▶ Dexamethasone 12 mg PO or IV daily</li> </ul> </li> </ul>	<div style="display: flex; flex-direction: column; align-items: center;"> <div style="border: 1px solid black; padding: 5px; margin-bottom: 10px;">Nausea and vomiting controlled</div> <div style="margin-bottom: 10px;">↓</div> <div style="border: 1px solid black; padding: 5px;">Nausea and/or vomiting uncontrolled</div> </div>	<div style="display: flex; flex-direction: column; align-items: center;"> <div style="margin-bottom: 10px;">Continue breakthrough medications, on a schedule, not PRN</div> <div style="margin-bottom: 10px;">↓</div> <div>Re-evaluate and consider dose adjustments and/or switching to a different therapy</div> </div>
		<p>Consider changing antiemetic therapy to higher level primary treatment for next cycle</p>

<sup>d</sup>See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (A-E-A).

<sup>e</sup>Order of listed antiemetics is alphabetical.

<sup>f</sup>Serotonin (5-HT<sub>3</sub>) antagonists may increase the risk of developing prolongation of the QT interval of the electrocardiogram. See Discussion.

<sup>n</sup>Monitor for dystonic reactions; use diphenhydramine 25-50 mg PO or IV either every 4 or every 6 h for dystonic reactions. If allergic to diphenhydramine use benztropine at 1-2 mg IV or IM x 1 dose, followed by oral dose of 1-2 mg daily or BID if needed to control the reaction.

<sup>r</sup>See Principles of Managing Breakthrough Treatment (A-E-B).

<sup>s</sup>Navari RM, Nagy CK, Gray SE. The use of olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. Support Care Cancer 2013;21:1655-1663.

**Note:** All recommendations are category 2A unless otherwise indicated.  
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

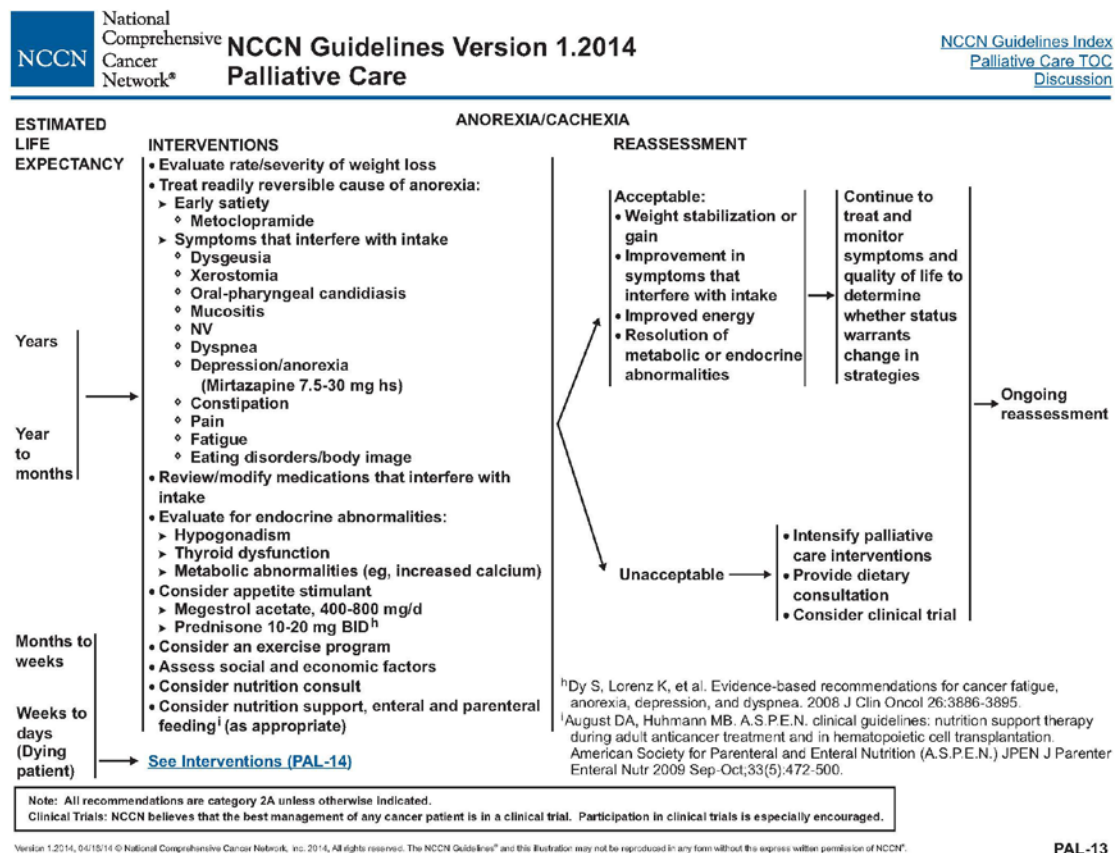
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**AE-6**

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## APPENDIX 8 NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY: ANOREXIA/CACHEXIA



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## APPENDIX 9 GLUTATHIONE (GSH)-, S-ADENOSYLMETHIONINE (SAM)-, OR N-ACETYLCYSTEINE (NAC)-CONTAINING PRODUCTS (REPRESENTATIVE LIST)

Product Name	Ingredient	Manufacturer/Brand	Strength	Dose Form	Other key ingredients
<b>Glutathione</b>					
Glutathione	glutathione	NOW Foods	500 mg	Vcaps	milk thistle, alpha lipoic acid
Glutathione	L-glutathione	NOW Foods	250 mg	Vcaps	
Glutathione reduced	glutathione	Jarrow Formulas	500 mg	capsules	
Reduced glutathione sublingual complex	glutathione	Source Naturals	50 mg	sublingual	
Glutathione reduced	glutathione	Bulk Supplements	10, 25, 50, 100, 250, 500, 1000 g	powder	
Reduced glutathione with alpha lipoic acid	Setria L-glutathione	Viva Labs	500 mg	capsules	alpha lipoic acid
Glutathione, Cysteine & C	glutathione, 50 mg L-cysteine, 200 mg vitamin C, 500 mg	Life Extension	750 mg	capsules	L-cysteine, vitamin C
Liposomal Glutathione	glutathione	Empirical Labs	4 mL	liquid	
Lypospheric GSH	glutathione	LivOn Laboratories	450 mg	packet	essential phospholipids from soy lecithin
Ivory Caps Skin Enhancement Formula	glutathione	Princeton Nutritional Systems	1500 mg	capsules	
Glutathione GOLD	S-acetyl glutathione	Health Naturally	200 mg	capsules	
Mega-Liposomal Glutathione	glutathione	Aurora NutraScience	750 mg	liquid	
L-Glutathione 500	L-glutathione	GNC	500 mg	capsules	
<b>N-acetylcysteine (NAC)</b>					
Acetadote for acetaminophen overdose	acetylcysteine	Cumberland Pharmaceuticals	IV	sterile solution, 200 mg/mL	
CerefolinNAC medical food for age-related memory loss	L-methylfolate vitamin B12 N-acetyl cysteine	PAMLAB, LLC	600 mg NAC	caplets	L-methylfolate vitamin B12

NAC	N-acetyl cysteine	NOW Foods	600 mg	capsules	selenium, molybdenum
N-A-C Sustain	N-acetyl L-cysteine	Jarrow Formulas	600 mg	capsules	
Best NAC Detox Regulators	N-acetyl cysteine	Doctor's Best	600 mg	capsules	selenium, 50 mg molybdenum, 50 mg
<b>S-adenosylmethionine (SAM)</b>					
SAM-e Complete	S-adenosylmethionine	Nature Made	400 mg	tablets	
SAMe	S-adenosyl-L-methionine	NOW Foods	400 mg	tablets	
Double Strength SAMe 400	S-adenosylmethionine	Doctor's Best	400 mg	tablets	
SAM-e 200	S-adenosylmethionine	Jarrow Formulas	200 mg	tablets	
SAMe	S-adenosyl-l-methionine	Source Naturals	400 mg	tablets	
SAMe	S-adenosyl-l-methionine	Source Naturals	200 mg	tablets	
SAMe	S-adenosylmethionine	Natrol	400 mg	enteric coated tablets	
SAMe	S-adenosyl-methionine	NOW Foods	200 mg	tablets	vitamin B-6, folic acid, vitamin B-12

<b>Clinical Study Protocol</b>	
<b>KCP-330-012</b>	
<b>A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) Plus Low-Dose Dexamethasone (Sd) in Patients with Multiple Myeloma Previously Treated with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib, and Daratumumab, and Refractory to Prior Treatment with Glucocorticoids, an Immunomodulatory Agent, a Proteasome Inhibitor, and the anti-CD38 mAb Daratumumab</b>	
<b>Study Name: STORM (Selinexor Treatment of Refractory Myeloma)</b>	
<b>Drug Development Phase:</b>	Phase 2b
<b>Investigational Product:</b>	Selinexor (KPT-330)
<b>Indication:</b>	Multiple myeloma (MM) previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and the anti-CD38 mAb daratumumab
<b>EudraCT Number:</b>	2016-003094-18
<b>Sponsor:</b>	Karyopharm Therapeutics Inc. 85 Wells Avenue Newton, MA 02459 USA Tel. + (617) 658-0600
<b>Protocol Date and Version:</b>	24 December 2014, Version 1.0 05 February 2015, Version 2.0 25 September 2015, Version 3.0 11 August 2016, Version 4.0- ROW (Rest of World) 06 February 2017, Version 4.1 US (Country-specific) 28 April 2017, Version 5.0 13 December 2017, Version 6.0
<b>CONDUCT</b> In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.	
<b>CONFIDENTIAL INFORMATION</b> This document is the sole property of Karyopharm Therapeutics Inc. (Karyopharm). This document and any and all information contained herein has to be considered and treated as strictly confidential. This document shall be used only for the purpose of the disclosure herein provided. No disclosure or publication shall be made without the prior written consent of Karyopharm.	

## PROTOCOL APPROVAL SIGNATURE PAGE

### SPONSOR: KARYOPHARM THERAPEUTICS INC.

I have read and understand the contents of this clinical protocol for Study No. KCP-330-012 dated 13 December 2017 and agree to meet all obligations of Karyopharm Therapeutics Inc., as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other Investigators of all relevant information that becomes available during the conduct of this Study.

Approved by:



**Sharon Shacham, PhD**  
**President and Chief Scientific Officer**  
**Karyopharm Therapeutics Inc.**

13 December 2017

**Date**

**Jatin Shah**

Digitally signed by Jatin Shah  
DN: cn=Jatin Shah, o=Karyopharm  
Therapeutics Inc., ou=Vice President,  
Clinical, email=jshah@karyopharm.com,  
c=US  
Reason: I am approving this document  
Date: 2017.12.14 18:35:51 -05'00'

**Jatin Shah, M.D.**  
**Vice President, Clinical Strategy**  
**Karyopharm Therapeutics Inc.**

13 December 2017

**Date**

## PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Study No. KCP-330-012 dated 13 December 2017 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the Study in accordance with current Good Clinical Practices, ICH E6, and applicable FDA regulatory requirements:

**Name of Principal Investigator:**

**Principal Investigator's Signature:** \_\_\_\_\_

**Principal Investigator's Name:** \_\_\_\_\_

**Institution:** \_\_\_\_\_

**Date:** \_\_\_\_\_

## PROTOCOL SYNOPSIS

Sponsor: Karyopharm Therapeutics Inc.	Investigational Product: Selinexor (KPT-330)	Developmental Phase: Phase 2b
<b>Title of Study:</b> A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) Plus Low-Dose Dexamethasone (Sd) in Patients with Multiple Myeloma Previously Treated with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib, and Daratumumab, and Refractory to Prior Treatment with Glucocorticoids, an Immunomodulatory Agent, a Proteasome Inhibitor, and the anti-CD38 mAb Daratumumab		
<b>Protocol Number:</b> KCP-330-012: STORM (Selinexor Treatment of Refractory Myeloma)		
<b>Indication:</b> Multiple myeloma previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and the anti-CD38 mAb daratumumab (penta-refractory MM)		
<b>Objectives:</b> <i>Primary:</i> Evaluate the efficacy (overall response rate [ORR]) for treatment with selinexor 80 mg plus low-dose dexamethasone (20 mg) (Sd) twice weekly (four-week cycles) in patients with MM previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and the anti-CD38 mAb daratumumab (herein referred to as penta-refractory MM).  ORR will include patients who experience partial response (PR), very good partial response (VGPR), complete response (CR), or stringent complete response (sCR), based on International Myeloma Working Group (IMWG) response criteria ( <a href="#">Kumar 2016</a> ) for patients with penta-refractory MM in Part 2 (Expansion).  <i>Secondary:</i> The following endpoints will be analyzed separately for (a) Part 1 patients with quad-refractory MM (i.e., previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, but not an anti-CD38 mab), (b) Part 1 patients with penta-refractory MM, and (c) Part 2 (expansion) patients with penta-refractory MM. Additionally, analyses of safety and tolerability will be performed on the overall population of patients from Parts 1 and 2 who received at least one dose of study treatment. <ul style="list-style-type: none"> <li>• Duration of response (DOR = Duration from first observation of at least PR to time of disease progression, or deaths due to disease progression, whichever occurs first. DOR will be censored for death due to any causes other than disease progression.</li> <li>• Clinical Benefit Rate (CBR = sCR + CR + VGPR + PR + minimal response [MR]), and duration of clinical benefit (Duration from first observation of at least MR to time of disease progression or death due to disease progression, whichever occurs first. Duration of clinical benefit will be censored for death due to any causes other than disease progression)</li> </ul>		

Sponsor: Karyopharm Therapeutics Inc.	Investigational Product: Selinexor (KPT-330)	Developmental Phase: Phase 2b
<ul style="list-style-type: none"> <li>• Disease Control Rate (DCR = CBR + stable disease [SD; for a minimum of 12 weeks])</li> <li>• Progression Free Survival (PFS = Duration from start of study treatment to PD or death [regardless of cause], whichever comes first)</li> <li>• Time to Progression (TTP = Duration from start of study treatment to time of disease progression) obtained with selinexor plus dexamethasone vs. TTP on most recent prior therapy</li> <li>• Time to next treatment (TTNT)</li> <li>• Overall Survival (OS = Duration from start of study treatment to death)</li> <li>• Quality of Life (QoL) using the Functional Assessment of Cancer Therapy - Multiple Myeloma (FACT-MM)</li> <li>• Safety and tolerability using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v 4.03.</li> <li>• Describe the PK properties of selinexor in this patient population (Part 1 only)</li> </ul> <p><i>Exploratory:</i></p> <p>The following endpoints may be analyzed separately for patients with penta-refractory MM and patients with quad-refractory MM (See the Statistical Analysis Plan; v 1.0, for a detailed description of the complete exploratory endpoints):</p> <ul style="list-style-type: none"> <li>• ORR, DOR, PFS, and OS in patients who were dosed with Sd for 4 weeks out of 4-week cycles (i.e., 8 doses per cycle) vs. patients who were dosed with selinexor for 3 weeks out of 4-week cycles (i.e., 6 doses per cycle)</li> <li>• ORR and TTNT for Sd vs. the patient's last treatment regimen</li> <li>• ORR, DOR, PFS, and OS in patients with Revised International Staging System (R-ISS) stage I vs. stage II vs. stage III)</li> <li>• Minimal residual disease (MRD) in patients who achieve CR and sCR, and selected patients who achieve VGPR</li> <li>• Correlative studies to evaluate response to treatment with selinexor as related to: <ul style="list-style-type: none"> <li>- Cytogenetic and fluorescent in situ hybridization (FISH) prognostic markers, including p53 abnormalities and chromosomal aberrations (e.g., del 17p, t(4;14), t(14;16), del 13) and other MM cytogenetic classifications</li> <li>- R-ISS stage (I vs. II vs. III)</li> <li>- Time since initial diagnosis of active myeloma</li> <li>- Lytic lesions as assessed by skeletal survey (or similar bone imaging)</li> </ul> </li> </ul>		
<p><b>Background and Study Rationale</b></p> <p><i>Background</i></p> <p>Multiple myeloma (MM) is the second most common hematological malignancy (after non-Hodgkin's lymphoma), representing 1% of all cancers and 2% of all cancer deaths. Despite the increased effectiveness of a variety of agents, nearly all patients will</p>		



Sponsor: Karyopharm Therapeutics Inc.	Investigational Product: Selinexor (KPT-330)	Developmental Phase: Phase 2b
<p>eventually relapse with their disease becoming drug-resistant. With over 12,600 deaths from MM anticipated in 2016 in the US alone, there is an unmet medical need for therapies in patients with relapsed and/or refractory (RR) MM that has progressed on available treatments.</p> <p>Selinexor is an orally bioavailable, selective inhibitor of nuclear export (SINE) compound that specifically blocks exportin 1 (XPO1). Selinexor and other SINE compounds have demonstrated anti-MM activity in preclinical studies. In the Phase-1 study, selinexor alone (all doses) showed an ORR of 5%, and with low-dose dexamethasone (Sd; all doses) the ORR was 32%. Therefore, the Sd regimen was carried forward into this ongoing Phase 2 study.</p> <p><i>Rationale for Expansion (protocol version 4.0)</i></p> <p>For Part 1 of this study, 78 patients with measurable RR MM have been evaluated (79 patients were enrolled, but 1 patient did not have measurable MM at baseline): 48 patients with quad-refractory MM (IMiDs and PIs) and 30 patients with penta-refractory MM (quad + anti-CD38 refractory). Patients were initially dosed with 6 doses of Sd per cycle, and this was increased to 8 doses of Sd per cycle. The ORR adjudicated by a four-physician Independent Review Committee (IRC) across all patients was 21% and the clinical benefit rate (CBR) is 33%. Similar ORR were seen in the patients with “penta” and “quad” MM, with higher CBR in patients who received 8 vs. 6 doses/cycle consistent with improved disease control with continuous dosing. The median duration of response (DOR) was ~5 months, with 9 patients continuing on study. There was a trend towards higher ORR in the 8-dose per cycle Sd regimen, with little difference in tolerability. Furthermore, there was a trend to increased time on study in patients with baseline hemoglobin (Hb) <math>\geq 8.5</math> gm/dL. Therefore, based on the current unmet medical need for patients with RR MM and these preliminary clinical results, this study is now being expanded to evaluate the efficacy and safety of twice-weekly Sd in patients with penta-refractory MM.</p>		
<p><b>Methodology:</b></p> <p>This is a Phase 2b, single-arm, open-label, multicenter study of Sd, dosed twice weekly each week in four-week cycles, in patients with penta-refractory MM (Parts 1 and 2) or quad-refractory MM (Part 1 only).</p> <p>The population for the primary efficacy analysis will contain only patients with penta-refractory MM enrolled in Part 2. Response results for patients with quad-refractory MM and patients with penta-refractory MM enrolled in Part 1 will be analyzed separately. Safety analyses will be performed on the overall population of patients who received at least one dose of study drug, presented overall and by study part, and separately for Part 1 penta-refractory and quad-refractory patient populations.</p> <p>Patients will receive treatment until progressive disease (PD), death, toxicity that cannot be managed by standard care, or withdrawal, whichever occurs first.</p>		
<p><b>Inclusion/Exclusion Criteria:</b></p> <p><i>Inclusion:</i></p>		

Sponsor: Karyopharm Therapeutics Inc.	Investigational Product: Selinexor (KPT-330)	Developmental Phase: Phase 2b
<p>Patients must meet all of the following inclusion criteria to be eligible to enroll in this study:</p> <ol style="list-style-type: none"> <li>Written informed consent in accordance with federal, local, and institutional guidelines.</li> <li>Age <math>\geq 18</math> years at the time of signing informed consent.</li> <li>Measurable MM based on IMWG guidelines as defined by at least one of the following: <ol style="list-style-type: none"> <li>Serum M-protein <math>\geq 0.5</math> g/dL by serum electrophoresis (SPEP) or, for IgA myeloma, by quantitative IgA</li> <li>Urinary M-protein excretion <math>\geq 200</math> mg/24 hours</li> <li>FLC <math>\geq 100</math> mg/L, provided that the FLC ratio is abnormal.</li> <li>If serum protein electrophoresis is felt to be unreliable for routine M-protein measurement, then quantitative Ig levels by nephelometry is acceptable.</li> </ol> </li> <li>Patients must have previously received <math>\geq 3</math> anti-MM regimens including: an alkylating agent, lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab, and a glucocorticoid. There is no upper limit on the number of prior therapies provided that all other inclusion/exclusion criteria are met.</li> <li>MM refractory to previous treatment with one or more glucocorticoids, parenteral PI (i.e., bortezomib and/or carfilzomib), IMiD (i.e., lenalidomide and/or pomalidomide), and daratumumab. Refractory is defined as <math>\leq 25\%</math> response to therapy, or progression during therapy or progression within 60 days after completion of therapy.</li> <li>Multiple myeloma that is refractory to the patient's most recent anti-MM regimen. (Documented severe intolerance to the patient's last therapy is allowed upon approval by the Medical Monitor.)</li> <li>Any clinically significant non-hematological toxicities (except for peripheral neuropathy as described in exclusion criterion #17) that patients experienced from treatments in previous clinical studies must have resolved to Grade <math>\leq 2</math> by Cycle 1 Day 1.</li> <li>Adequate hepatic function within 21 days prior to Cycle 1 Day 1: total bilirubin <math>&lt; 2\times</math> upper limit of normal (ULN) (except patients with Gilbert's syndrome who must have a total bilirubin of <math>&lt; 3\times</math> ULN), AST <math>&lt; 2.5\times</math> ULN and ALT <math>&lt; 2.5\times</math> ULN.</li> <li>Adequate renal function within 21 days prior to Cycle 1 Day 1: estimated creatinine clearance of <math>\geq 20</math> mL/min, calculated using the formula of Cockcroft and Gault.</li> <li>Female patients of childbearing potential must agree to use 2 methods of contraception (including 1 highly effective and 1 effective method of contraception) and have a negative serum pregnancy test at Screening. Male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose of study treatment.</li> <li>Eastern Cooperative Oncology Group (ECOG) Performance Status of <math>\leq 2</math>.</li> <li>Adequate hematopoietic function within 21 days prior to Cycle 1 Day 1 (See Exclusion Criterion #20 for transfusion washout periods for RBCs and platelets): <ol style="list-style-type: none"> <li>Total WBC count <math>&gt; 1,000/\text{mm}^3</math></li> <li>ANC <math>\geq 1000/\text{mm}^3</math></li> </ol> </li> </ol>		

Sponsor: Karyopharm Therapeutics Inc.	Investigational Product: Selinexor (KPT-330)	Developmental Phase: Phase 2b
<p>c. Platelet count <math>\geq 75,000/\text{mm}^3</math> (patients in whom <math>&lt; 50\%</math> of bone marrow nucleated cells are plasma cells) or <math>\geq 50,000/\text{mm}^3</math> (patients in whom <math>\geq 50\%</math> of bone marrow nucleated cells are plasma cells. [Platelet transfusions <math>&lt; 1</math> week prior to Cycle 1 Day 1 are prohibited (see below).]</p> <p>13. Hemoglobin level <math>\geq 8.5</math> g/dL. In certain cases, patients with stable baseline hemoglobin level <math>&gt; 8.0</math> may be included following approval by the Medical Monitor. [Red blood cell transfusions <math>&lt; 2</math> weeks prior to Cycle 1 Day 1 are prohibited (see below).]</p> <p>14. Confirmation of patient eligibility for specific key criteria for study participation with the Medical Monitor.</p> <p><i>Exclusion Criteria:</i></p> <ol style="list-style-type: none"> <li>1. Active smoldering MM.</li> <li>2. Active plasma cell leukemia.</li> <li>3. Documented systemic amyloid light chain amyloidosis.</li> <li>4. Active central nervous system (CNS) MM.</li> <li>5. Pregnancy or breastfeeding.</li> <li>6. Radiation, chemotherapy, or immunotherapy or any other anticancer therapy <math>\leq 2</math> weeks prior to Cycle 1 Day 1, and radio-immunotherapy 6 weeks prior to Cycle 1 Day 1.</li> <li>7. Active graft vs. host disease (after allogeneic stem cell transplantation) at Cycle 1 Day 1</li> <li>8. Life expectancy of <math>&lt; 4</math> months.</li> <li>9. Major surgery within four weeks prior to Cycle 1 Day 1.</li> <li>10. Active, unstable cardiovascular function: <ol style="list-style-type: none"> <li>a. Symptomatic ischemia, or</li> <li>b. Uncontrolled clinically-significant conduction abnormalities (e.g., patients with ventricular tachycardia on antiarrhythmics are excluded; patients with 1st degree atrioventricular (AV) block or asymptomatic left anterior fascicular block/right bundle branch block (LAFB/RBBB) will not be excluded), or</li> <li>c. Congestive heart failure (CHF) of New York Heart Association (NYHA) Class <math>\geq 3</math>, or</li> <li>d. Myocardial infarction (MI) within 3 months prior to Cycle 1 Day 1.</li> </ol> </li> <li>11. Active, uncontrolled hypertension.</li> <li>12. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to first dose.</li> <li>13. Known HIV seropositive.</li> <li>14. Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface antigen).</li> <li>15. Prior malignancy that required treatment, or has shown evidence of recurrence (except for non-melanoma skin cancer or adequately treated cervical carcinoma in situ) during the 5 years prior to enrollment. Cancer treated with curative intent <math>&gt; 5</math> years previously and without evidence of recurrence will be allowed.</li> <li>16. Active GI dysfunction interfering with the ability to swallow tablets, or any GI dysfunction that could interfere with absorption of study treatment.</li> </ol>		

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<p>17. Grade <math>\geq 3</math> peripheral neuropathy, and Grade <math>\geq 2</math> painful neuropathy, within 21 days prior to Cycle 1 Day 1.</p> <p>18. Serious, active psychiatric or medical conditions which, in the opinion of the Investigator, could interfere with treatment.</p> <p>19. Participation in an investigational anti-cancer study within 21 days prior to Cycle 1 Day 1.</p> <p>20. Receipt of transfusions as follows:</p> <ol style="list-style-type: none"> <li>Platelet infusion within 1 week prior to Cycle 1 Day 1.</li> <li>RBC transfusion within 2 weeks prior to Cycle 1 Day 1.</li> </ol> <p>21. Receipt of the following blood growth factors within 2 weeks prior to Cycle 1 Day 1: Granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), erythropoietin (EPO), or megakaryocyte growth factor.</p> <p>22. Known intolerance to or contraindication for glucocorticoid therapy at Cycle 1 Day 1.</p> <p>23. Prior exposure to a SINE compound, including selinexor.</p> <p>24. Unable or unwilling to comply with protocol requirements, including providing a 24-hour urine samples at the required study time points.</p> <p><i>Documentation Requirements</i></p> <p>For enrollment consideration, patients may be eligible if they have <i>documented evidence</i> of previous treatment for MM that substantiates disease status as follows:</p> <ul style="list-style-type: none"> <li>Refractory to a glucocorticoid</li> <li>Refractory to lenalidomide and/or pomalidomide (only 1 required) <i>and</i> evidence of prior treatment* with <i>both</i> lenalidomide and pomalidomide</li> <li>Refractory to bortezomib and/or carfilzomib (only 1 required) <i>and</i> evidence of prior treatment* with <i>both</i> bortezomib and carfilzomib</li> <li>Refractory to daratumumab</li> </ul> <p>* Prior treatment is defined as either refractory, treatment with <math>\geq 2</math> cycles, or documented severe intolerance.</p> <p><i>Documented evidence will include at least one of the following:</i></p> <ol style="list-style-type: none"> <li>Medical records that support start and stop dates (month/year) of prior treatment (both dose and schedule), best response on prior treatment and, if applicable, date of progression (including both dose and schedule at the time of progression).</li> <li>Myeloma marker values (SPEP, UPEP, Immunoglobulin, FLC) at the time of prior treatment start, stop and time of progression (accompanied by #1).</li> <li>Formal, signed physician letter by Investigator (on hospital/clinic letterhead), to be included in the patient's medical and research record, indicating start/stop dates of prior treatment (both dose and schedule), best response on treatment and, if applicable, date of progression (including both dose and schedule at the time of progression).</li> <li>Formal, signed physician letter from referring physician (on hospital/clinic letterhead), to be included in the patient's medical and research record, that includes prior treatment history indicating start/stop dates of prior treatment (both dose and schedule), best response on prior treatment and, if applicable, date of progression (including both dose and schedule at the time of progression).</li> </ol>		

Sponsor: Karyopharm Therapeutics Inc.	Investigational Product: Selinexor (KPT-330)	Developmental Phase: Phase 2b
<b>Test Product, Dose and Mode of Administration:</b> <p>Selinexor will be given at an oral fixed milligram (mg) dose of 80 mg twice weekly each week for four-week cycles (total of 8 selinexor doses per cycle).</p> <p>Dexamethasone 20 mg will be given with each dose of selinexor. If a patient develops partial intolerance to glucocorticoids (as determined by the Investigator) during the study, a minimum dose of dexamethasone 10 mg is permitted. If any patient is not able to tolerate this dose, then a potential discontinuation or further decrease in dosage would be allowed after a discussion with the Medical Monitor on a case by case basis.</p> <p>In select cases (e.g., for patients showing SD, MR or PR and tolerating treatment particularly well), the selinexor dose may be increased by 20 mg (i.e., to 100 mg twice weekly) after consultation with the Medical Monitor. The dose level for an individual patient may be escalated based on efficacy considerations after completing a minimum of 2 cycles of study therapy. However, in no case may the dose for a given patient exceed 70 mg/m<sup>2</sup>.</p>		
<b>Concomitant Medications:</b> <p>To minimize nausea, unless contraindicated, all patients should receive 5-hydroxytryptamine (5-HT<sub>3</sub>) antagonists (e.g., ondansetron 8 mg or equivalent) starting on Day 1 before the first dose of selinexor and continued 2-3 times daily, as needed. Alternative anti-emetic agents should be used if the patient does not tolerate 5-HT<sub>3</sub> antagonists. Additional anti-nausea and anti-anorexia agents may be given as needed (per National Comprehensive Cancer Network<sup>®</sup> [NCCN] Clinical Practice Guidelines<sup>®</sup> for Antiemesis and NCCN Clinical Practice Guidelines<sup>®</sup> for Palliative Care). Patients will also receive therapy as needed to mitigate selinexor side effects, as part of best supportive care. Blood product transfusions, antimicrobials, and (as appropriate) growth factors including granulocyte colony-stimulating factors for neutropenia, erythropoietins for anemia, and/or platelet-stimulating factors for thrombocytopenia are also permitted.</p> <p>Patients may continue their baseline medication(s). Medications to treat concomitant diseases such as diabetes, hypertension, etc., are allowed. Patients will also receive concomitant medications that are medically necessary as standard care to treat symptoms, AEs and intercurrent illnesses. Patients may receive red blood cell or platelet transfusions, or blood growth factors, if clinically indicated, per institutional guidelines.</p> <p>Concurrent therapy with any other approved or investigational anti-cancer therapy is not allowed. Other investigational agents should not be used during the study.</p>		
<b>Study Numbers:</b> <p>Approximately 210 patients will be enrolled overall, including 79 patients (with quad-refractory MM and penta-refractory MM) in Part 1 and ~130 patients (with penta-refractory MM only) in Part 2 (to achieve the target population size of N = 122 for the primary efficacy analysis).</p>		
<b>Study Duration:</b> <p>The enrollment period for this study is expected to be approximately 24 months. There is no maximum treatment duration for the study or pre-defined number of treatment cycles</p>		

Sponsor: Karyopharm Therapeutics Inc.	Investigational Product: Selinexor (KPT-330)	Developmental Phase: Phase 2b
per patient. The study will end when all patients have completed the one-year Follow-up Period (i.e., when the last patient has expired, been followed for 12 months after last dose of study drug, been lost to follow-up, or has withdrawn consent, whichever occurs first).		
<p><b>Criteria for Evaluation:</b></p> <p><i>Safety:</i></p> <p>Safety and tolerability will be evaluated by adverse event (AE) reports, physical examinations, and laboratory safety evaluations. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 will be used for grading of AEs. For all AEs, Investigators will provide their assessment of causality with study treatment as either related or not related.</p> <p><i>Efficacy:</i></p> <p>Response will be assessed per IMWG for MM (<a href="#">Kumar 2016</a>) as:</p> <ul style="list-style-type: none"> <li>• Stringent complete response (sCR)</li> <li>• Complete response (CR)</li> <li>• Very good partial response (VGPR)</li> <li>• Partial response (PR)</li> <li>• Stable disease (SD)</li> <li>• Progressive disease (PD)</li> <li>• Minimal response (MR)</li> </ul> <p>Efficacy endpoints include the following:</p> <ul style="list-style-type: none"> <li>• ORR and DOR</li> <li>• CBR and duration of clinical benefit</li> <li>• DCR and duration of disease control</li> <li>• PFS</li> <li>• OS</li> <li>• TTP</li> <li>• QoL using the FACT-MM</li> </ul> <p><i>Pharmacokinetics/Pharmacodynamics:</i></p> <ul style="list-style-type: none"> <li>• Pharmacokinetic (PK) properties of selinexor in patients enrolled in Part 1 (only)</li> <li>• Pharmacodynamic (PDn) changes in selected biomarkers following treatment</li> <li>• Minimal residual disease (MRD) in patients who achieve sCR</li> </ul>		



Sponsor: Karyopharm Therapeutics Inc.	Investigational Product: Selinexor (KPT-330)	Developmental Phase: Phase 2b
<b>Criteria for Treatment Discontinuation:</b> <p>At the discretion of the Investigator, the Investigator may remove a patient from study treatment for any of the following reasons:</p> <ul style="list-style-type: none"><li>• Disease progression</li><li>• Unacceptable AE(s) or failure to tolerate the study treatment</li><li>• Patient decides to discontinue study therapy and withdraws consent</li><li>• Any medically appropriate reason or significant protocol violation, per the Investigator.</li></ul> <p>Patients may decide to discontinue study treatment for any reason. Patients who elect to discontinue study treatment should be encouraged to continue in the study so that follow-up information on disease progression and survival status may be obtained. However, patients may elect to withdraw consent and decline further participation in the study. The reason for discontinuation should be clearly documented. If clinical or biological progression, study data must be available. If the patient withdraws consent or is removed by the study Investigator, the reason for withdrawal should be documented.</p>		
<b>Statistical Methods:</b> <i>Sample Size Justification:</i> <p>The sample size for this study addresses the primary study objective of evaluating the clinical effect of selinexor 80 mg plus dexamethasone 20 mg (Sd) in patients with penta-refractory MM by reference to a minimal threshold level for ORR, set to 0.10 (10%). Note that the original sample size estimation for the study in Part 1 was based on clinical assumptions for patients with quad-refractory MM, and the assumptions have been updated for patients with penta-refractory MM.</p> <p>Based on preliminary evidence from an ongoing Phase 1 trial (KCP-330-001), it is believed that Sd may exhibit substantial efficacy; therefore, the statistical test associated with the comparison to the threshold will maintain a Type I error rate of 0.025, one-sided. For the primary efficacy analysis, a sample size of 122 patients with penta-refractory MM will allow a one-sided test at <math>\alpha=0.025</math> to detect an ORR of <math>\geq 0.20</math> against the threshold ORR of 0.10, with 90% power.</p> <p>Overall, a total of ~210 patients will be enrolled, including ~130 newly enrolled patients with penta-refractory MM (Part 2; Versions <math>\geq 4.0</math>) for the primary analysis and ~80 previously enrolled patients in Part 1 (~30 patients with penta-refractory MM and ~50 patients with quad-refractory MM enrolled under Versions <math>&lt; 4.0</math>) for additional secondary and exploratory analyses.</p>		

Sponsor: Karyopharm Therapeutics Inc.	Investigational Product: Selinexor (KPT-330)	Developmental Phase: Phase 2b
<p><i>Efficacy Evaluation:</i></p> <p>The primary statistical analysis of efficacy will be performed on ORR (proportion of patients who achieve sCR, CR, VGPR, or PR) using the modified intent-to-treat (mITT) population, defined as Part 2 patients with penta-refractory MM who met all eligibility criteria (or did not meet all eligibility criteria but received waiver from Sponsor to participate in the study), and received at least 1 dose of study treatment (partial or complete). The primary analysis will be performed on the Part 2 patients with penta-refractory MM only.</p> <p>A per-protocol (PP) population will consist of all patients in the mITT population who meet the following criteria:</p> <ul style="list-style-type: none"><li>• Have selinexor compliance <math>\geq 70\%</math>,</li><li>• Have at least 1 adequate post-baseline response assessment unless died or withdrew from study before that.</li><li>• No major protocol violations that would compromise the assessment of efficacy. The list of major protocol violations that affect statistical analysis will be finalized before database lock.</li></ul> <p>The PP population will be used for supportive inferences concerning efficacy.</p> <p>Secondary and exploratory endpoints will be assessed using the mITT population and the PP population. Time-to-event endpoints (including DOR) will be assessed using Kaplan-Meier methods.</p> <p>Quality of life (QoL) will be assessed using the Functional Assessment of Cancer Therapy with MM-specific subscale (FACT-MM). The trial outcomes index (TOI) will be the primary measurement of interest, comprised of the physical and functional subscales plus the MM-specific subscale.</p> <p><i>Safety Evaluation:</i></p> <p>Safety analyses will be performed on the overall population of patients who received any amount of study treatment, presented overall and by study part.</p>		



**Table 1: Schedule of Assessments and Study Activities**

Activity/Assessment	Screening	Cycle 1				Cycle 2		Cycles $\geq 3$	End-of-Treatment (EoT) Visit	Safety Follow-up Call	Durability of Response and Survival Follow-up <sup>15</sup>
	Day -21 to Day -1	Day 1	Day 3 <sup>14</sup>	Day 8	Day 15	Day 1	Day 15	Day 1	$\leq 14$ Days Post Last Dose	30 Days Post-Last Dose	Every 3 mo.
		-1 day	+1 day	$\pm 1$ day	$\pm 1$ day	$\pm 2$ days	$\pm 2$ days	$\pm 2$ days		+ 7 days	$\pm 14$ days
Informed consent <sup>1</sup>	X										
Inclusion/exclusion criteria	X										
Demographics	X										
Medical history <sup>2</sup>	X	X									
Patient height	X										
Patient weight	X	X		X	X	X	X	X	X		
Body Surface Area (BSA) <sup>3</sup>	X										
Physical examination, full including vital signs <sup>4</sup>	X								X		
Physical examination, symptom-directed, including vital signs <sup>4</sup>		X		X	X	X	X	X			
ECOG <sup>5</sup>	X					X		X	X		
Echocardiogram or MUGA <sup>6</sup>	X										
12-lead ECG	X								X		
Ophthalmic exam <sup>7</sup>	X								X		
Clinical Labs											
Urinalysis <sup>5</sup>	X								X		
CBC with differential <sup>5</sup>	X				X	X	X	X	X		
TSH <sup>5</sup>	X								X		
Complete serum chemistry <sup>5</sup>	X					X		X	X		
Limited serum chemistry				X	X		X				
Coagulation tests <sup>5</sup>	X								X		

Activity/Assessment	Screenin g	Cycle 1				Cycle 2		Cycles ≥ 3	End-of-Treatment (EoT) Visit	Safety Follow-up Call	Durability of Response and Survival Follow-up <sup>15</sup>
	Day -21 to Day -1	Day 1	Day 3 <sup>14</sup>	Day 8	Day 15	Day 1	Day 15	Day 1	≤ 14 Days Post Last Dose	30 Days Post-Last Dose	Every 3 mo.
		-1 day	+1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days		+ 7 days	± 14 days
Serum hCG pregnancy test <sup>8</sup>	X					X (D1 of each cycle only)		X (D1 of each cycle only)	X		
C-reactive protein	X	X				X		X	X		
Multiple Myeloma Assessments											
SPEP and serum protein immunofixation <sup>9</sup>	X	X				X		X	X		X
UPEP (24-hr urine for total protein) and urine protein immunofixation <sup>9</sup>	X	X				X		X	X		X
Quantitative Ig levels <sup>9</sup>	X	X				X		X	X		X
Serum FLC <sup>9</sup>	X	X			X	X	X	X	X		X
β <sub>2</sub> -microglobulin	X								X		
Skeletal survey <sup>10</sup>	X					(X)		(X)	X		(X)
Plasmacytoma assessment <sup>11</sup>	X					(X)		(X)	X		(X)
Bone marrow aspirate <sup>12</sup>	X					(X)		(X)			(X)
Bone marrow core biopsy <sup>13</sup>	X					(X)					
FACT-MM questionnaire	X					X		X	X		
Study drug dosing		Selinexor 80 mg + dexamethasone 20 mg (both twice weekly) for 4 weeks (each week) of 4-week cycles									
Adverse events <sup>16</sup>	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X		
Nutritional consultation	X										
Telephone contact <sup>14</sup>			X							X	X
Antineoplastic therapy after EoT									X	X	X

(X) indicates that additional information is provided in the footnotes. Merged cells indicate that the procedure may be performed during either Screening or the C1D1 visit.

Abbreviations: BSA = body surface area; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoT = End of Treatment; Ig = immunoglobulin; MM = multiple myeloma; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; CBC = complete blood count; FLC = free light chain.

- <sup>1</sup> Prior to the first study-specific measure.
- <sup>2</sup> Including details of all prior anti-myeloma therapies. Includes baseline symptoms as well as a detailed history of prior cancer therapies, especially MM therapies, including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness. Results of pre-screening MM assessments at Day -30 (window: Screening – 2 weeks) and Day -60 ( $\pm 15$  days) will be provided.
- <sup>3</sup> Body Surface Area (BSA) will be calculated by *Dubois 1916* or *Mosteller 1987* method during Screening and prior to any dose escalation. No patient may receive a dose of selinexor  $> 70$  mg/m<sup>2</sup>.
- <sup>4</sup> Complete physical examination (PE) during Screening and EoT visit. Limited PEs during the study should be symptom directed. All PEs to include vital signs (blood pressure, pulse and body temperature).
- <sup>5</sup> The following procedures may be performed at Screening or pre-dose on C1D1 and as shown in the Schedule during the study: ECOG performance assessment, echocardiogram or MUGA scan, 12-lead ECG, ophthalmic exam, urinalysis, CBC with differential, TSH, complete serum chemistry, coagulations tests, and nutritional consultation.
- <sup>6</sup> Echocardiogram or MUGA scan at Screening and as clinically indicated during the study.
- <sup>7</sup> A full ophthalmic examination will include, prior to dilation, best corrected visual acuity, slit lamp examination including tonometry, following dilation; funduscopy and slit lamp to document lens clarity.
- <sup>8</sup> For females of childbearing potential; negative serum hCG pregnancy test must be obtained within 3 days before the first dose of study treatment. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of Cycles  $\geq 2$  and at the EoT Visit (serum hCG). Pregnancy testing may also be performed as clinically indicated during the study.
- <sup>9</sup> Response criteria include SPEP, UPEP (24-hr urine), serum and urine immunofixation, quantitative Ig levels, and serum FLC assay on C1D1 and must be taken either on Day -1 or pre-dose on C1D1. The assessments must be repeated at the time of disease progression or suspected response in order to confirm response. Note: For patients who achieve CR or sCR, as assessed by the local lab, assessments will be confirmed by a central lab using portions of the samples collected. See the *Study Manual* for additional information. Results of pre-screening MM assessments at Day -30 (window: Screening – 2 weeks) and Day -60 ( $\pm 15$  days) will be provided as part of Medical History.
- <sup>10</sup> Skeletal survey to be performed using x-rays per institutional guidelines. If x-rays are used, they should include a lateral radiograph of skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. If clinically appropriate, MRI, CT, or PET/CT, with tumor measurements, may be used instead of, or in addition to, x-rays. If bone lesions or plasmacytomas are observed at baseline, their number and size should be recorded in the CRF. Bone lesions and/or plasmacytomas seen at baseline using imaging should be assessed as clinically appropriate per Investigator's discretion during the study. Skeletal survey results will be read by the local laboratory.
- <sup>11</sup> If plasmacytomas are detected at baseline by PE, they should be measured and recorded, and re-assessed during the PE on Day 1 of each cycle, EoT visit, and every 3 months (if clinically appropriate) during follow-up.
- <sup>12</sup> Bone marrow aspirate:
  - a. At Screening for Karyotyping and FISH analysis to confirm diagnosis and classify MM sub-type (required per standard of care).
  - b. High-risk cytogenetic analyses and separation of CD138- and CD138+ cell fractions for subsequent genomic, transcriptomic and/or proteomic analyses (exploratory PDn study)
  - c. MRD analysis (exploratory PDn study) at response for CR, sCR, or potential CR in patients with FLC only or unequivocal IFE.

- <sup>13</sup> Bone marrow biopsy:
- a. At time of response (as soon as feasible after SPEP, UPEP, FLC, and quantitative Ig levels are known) to confirm CR and sCR, per IMWG, by a central lab. See the *Study Manual* for additional information.
  - b. Two additional *optional* bone marrow core biopsies, (per Investigator's discretion), one each at baseline and after one cycle of treatment are requested and may be used for PDn exploratory studies. If sufficient sample is available, one portion of each biopsy should be fixed in 10% formalin and another portion should be fresh frozen. An archival sample taken within 30 days prior to C1D1 may be used in lieu of the baseline sample. A second sample should be obtained on C2D1 (+ 5 days) only from patients for whom a baseline sample (including archival) is also available.
- <sup>14</sup> Telephone call (or visit) with patient to evaluate supportive care medications, concomitant medications and adverse events, and to adjust supportive care as appropriate. The telephone contact with the patient must take place on C1D3 (following administration of first dose of selinexor on C1D1).
- <sup>15</sup> After treatment discontinuation, if possible, for patients who are not progressing, SPEP with serum immunofixation, UPEP (24 hr.) with urine protein immunofixation, serum FLC, and quantitative Ig levels (and physical examinations and imaging for bone lesions and plasmacytomas, if clinically appropriate) should be performed every 3 months for 1 year to assess durability of response. If these assessments cannot be performed, and for patients with PD, a telephone call will be made to the patient (or the patient's family) every 3 months for one year to inquire about the patient's survival, MM status, well-being, and information on any antineoplastic therapies utilized since discontinuation of selinexor study treatment.
- <sup>16</sup> Serious adverse events that occur after signing patient signs the ICF (including prior to first dose on C1D1) and adverse events that occur after first dose on C1D1.

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## LIST OF ABBREVIATIONS

Abbreviation	Definition
5-HT3	5-hydroxytryptamine
ACS	acute cerebellar syndrome
AE	adverse event
ALT	alanine transaminase (SGPT)
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCT	autologous stem cell transplantation
AST	aspartate transaminase (SGOT)
AUC <sub>last</sub>	area under the curve, first-last measurement
AUC <sub>(0-∞)</sub>	area under the curve, time zero to last
AV	arterioventricular
bid	twice daily
BMSC	bone marrow stroma cells
BP	blood pressure
BSA	body surface area
BSC	best supportive care
BUN	blood urea nitrogen
°C	degrees Centigrade
CBC	complete blood count
CBR	clinical benefit rate
CD	cluster of differentiation
anti-CD38 mAb	monoclonal antibodies against CD38 antigen expressed by leukocytes
CD-ROM	compact disc, read-only-memory
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CLL	chronic lymphocytic leukemia
Cm	centimeter
C <sub>max</sub>	maximum serum concentration
CML	chronic myeloid leukemia
CNS	central nervous system
CR	complete response
CRA	clinical research associate

<b>Abbreviation</b>	<b>Definition</b>
CRF	case report form
CRM1	chromosomal region maintenance protein 1
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
cyclo	cyclophosphamide
DCR	disease control rate
Dex	dexamethasone
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DOR	duration of response
Dox	doxorubicin
DSMC	Data Safety Monitoring Committee
DT	dexamethasone + thalidomide
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
F%	oral bioavailability
°F	degrees Fahrenheit
FACT-G	Functional Assessment of Cancer Therapy (general version)
FACT-MM	Functional Assessment of Cancer Therapy - Multiple Myeloma
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin embedded
FISH	fluorescent in situ hybridization
FLC	free light chain (kappa/lamba ratio)
FLT3	fms-like tyrosine kinase
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GM-CSF	granulocyte macrophage-colony stimulating factor

<b>Abbreviation</b>	<b>Definition</b>
GRP	growth regulatory protein
GSH	glutathione
Hb	hemoglobin
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPLC/MS-MS	high performance liquid chromatography/tandem mass spectrometry
hr	hour
IC <sub>50</sub>	inhibitory concentration, 50% (half maximal inhibitory concentration)
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN $\alpha$	interferon alpha
IFN $\gamma$	interferon gamma
IgA	immunoglobulin A
IgVH	immunoglobulin heavy chain variable region
IL-1 $\alpha$	interleukin 1 alpha
IL-6	interleukin 6
IL-8	interleukin 8
IL-10	interleukin 10
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
INR	international normalization ratio
IRC	Independent Review Committee
ISS	International Staging System
ITT	intent-to-treat
IV	intravenous
kg	kilogram
KM	Kaplan-Meier
LAFB	left anterior fascicular block
LDH	lactate dehydrogenase
LMW	low molecular weight

<b>Abbreviation</b>	<b>Definition</b>
LOCSIII	Lens Opacities Classification System
m <sup>2</sup>	square meters
MAb	monoclonal antibody
MCP1	monocyte chemo-attractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	myocardial infarction
min	minute
miRNA	microRNA
mL	milliliter
mITT	modified intent-to-treat
MM	multiple myeloma
mmHg	millimeters of mercury
MTD	maximum tolerated dose
MR	minimal response
mRNA	messenger ribonucleic acid
MUGA	multiple gated acquisition
5'NT	5'-nucleotidase
NAC	N-acetylcysteine
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NES	nuclear export sequences
NHL	non-Hodgkin's lymphoma
NK1R	neurokinin 1 receptor
NPC	nuclear pore complex
NPM1	nucleophosmin
NYHA	New York Heart Association
OPG	osteoprotegerin
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PDn	pharmacodynamic
PE	physical examination

<b>Abbreviation</b>	<b>Definition</b>
PFS	progression free survival
PI	proteasome inhibitor (within drug treatment context)
PI	principal investigator (within clinical context)
PK	pharmacokinetic
po	by mouth
PP	per protocol
PPI	proton pump inhibitor
PR	partial response
prn	as needed
PT	prothrombin time
qAM	every morning
qd	once daily
qhs	at bedtime
qid	four times daily
QoL	quality of life
qRT-PCR	quantitative real time polymerase chain reaction
RBBB	right bundle branch block
RBC	red blood cell
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RPPA	reverse phase protein array
RR	resistant/refractory
RT	Richter's transformation
SAE	serious adverse event
SAM	S-adenosylmethionine
sCR	stringent complete response
Sd	selinexor 80 mg plus dexamethasone 20 mg ("low-dose" dexamethasone)
SD	stable disease
SIADH	Syndrome of Inappropriate Antidiuretic Hormone Secretion
SINE	selective inhibitor of nuclear export
SOC	standard of care (within treatment context)
SOC	system organ class (within adverse event context)
SOP	standard operating procedure
SPEP	serum protein electrophoresis



<b>Abbreviation</b>	<b>Definition</b>
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
tid	three times daily
TK	toxicokinetic
T <sub>max</sub>	time to maximum serum concentration
TNF $\alpha$	tumor necrosis factor alpha
TOI	trial outcomes index
TSH	thyroid stimulating hormone
TSP	tumor suppressor protein
TTP	time to progression
TUNEL	terminal deoxyribonucleotidyl transferase-dUTP nick end labeling
ULN	upper limit of normal
UPEP	urine protein electrophoresis
VEGF $\alpha$	vascular endothelial growth factor alpha
VGPR	very good partial response
WBC	white blood cell
XPO1	exportin 1

## 1. OVERVIEW

Multiple myeloma (MM) is the second most common hematological malignancy (after non-Hodgkin's lymphoma), representing 1% of all cancers and 2% of all cancer deaths. Despite the increased effectiveness of first-line agents, the majority of patients will eventually relapse and become resistant to all classes of available anti-MM therapies. With over 30,000 new cases and approximately 12,600 deaths from MM anticipated in 2016 in the USA alone ([ACS 2016](#)), there remains a need for novel therapies for the treatment of refractory MM that can improve the overall survival rate.

Selinexor is a Selective Inhibitor of Nuclear Export (SINE) compound that binds and inactivates Exportin 1 (XPO1), thereby forcing the nuclear retention of key tumor suppressor proteins (TSPs). XPO1 protein levels are significantly elevated in MM, leading to the nuclear exclusion of TSPs, the glucocorticoid receptor (GR), and enhanced translation of certain oncogene mRNAs ([Tai 2014](#)). Transient retention of TSPs in the nucleus at high levels via XPO1 blockade activates their cell cycle checkpoint and genome surveying actions. This leads to the death of nearly all types of malignant cells, whereas normal cells undergo transient cell cycle arrest and recovery when the export block is released. XPO1 also exports the GR, leading to attenuation of its transcriptional activity. In the presence of glucocorticoids, XPO1 blockade leads to nuclear accumulation and activation of the GR. In addition, XPO1 inhibition leads to the nuclear entrapment of cap-binding protein (eIF4E)-dependent oncogene mRNAs, thus preventing their translation into proteins in the cytoplasm. In this way, SINEs lead to reduction in key oncoproteins such as c-Myc, Cyclin D, hDM2 and others. The reactivation of multiple TSP pathways as well as glucocorticoid signaling, along with reduced translation of key oncoproteins through inhibition of a non-redundant, single protein, i.e., XPO1, represents a novel approach to the treatment of neoplastic diseases including those with multiple genomic alterations and resistance mechanisms.

Single-agent Phase 1 studies with oral selinexor have been conducted in advanced hematological malignancies including MM, acute myeloid leukemia (AML), non-Hodgkin's leukemia (NHL) and chronic lymphocytic leukemia (CLL) (KCP-330-001), in solid tumors (KCP-330-002), and in soft tissue and bone sarcomas (KCP-330-003). Broad antitumor activity has been observed in all of these studies. In addition, Phase 2 studies are ongoing in MM, AML, DLBCL, Richter's transformation, glioblastoma, gynecological malignancies, and dedifferentiated liposarcoma (DDLs). More than 2,000 patients with objectively progressing tumors at study entry have received selinexor as of 31 March 2017.

The most frequently reported side effects of selinexor seen in clinical studies to date are anorexia, fatigue, nausea, vomiting, and thrombocytopenia. These adverse events (AEs) may be mitigated or eliminated with standard supportive care. In addition, their prevalence and intensity typically decline after 4-8 weeks of treatment. Selinexor treatment is not associated with significant major organ toxicity. Moreover, clinically-relevant cumulative toxicities have not been observed during long term treatment, with more than 28 patients receiving single-agent selinexor for over 1 year and 6 patients for over 2 years. Please see the current [Selinexor Investigator's Brochure \(IB\)](#) for more information.

Selinexor has shown single-agent, durable, anti-cancer activity in patients with multiple RR hematologic and solid tumor malignancies, including MM, at doses of  $\geq 6$  mg/m<sup>2</sup> body surface area (BSA) in initial Phase 1 dose-escalation studies. In addition, results from a small number of patients suggests that selinexor in combination with dexamethasone 20 mg has increased efficacy in RR MM patients relative to selinexor alone ([Chen 2014](#), *Data on file*).

In the current study, patients will receive low-dose dexamethasone (20 mg) to both improve the tolerability of selinexor and provide additional efficacy benefit as selinexor has been shown to activate glucocorticoid signaling through its receptor. Dexamethasone has been shown in previous studies to be an effective prophylactic treatment for the common AEs of selinexor described above. While untreated MM is exquisitely sensitive to glucocorticoids, this benefit wanes over time with treatment, which usually includes glucocorticoids in combination therapy. Patients with MM which has relapsed after multiple treatments are unlikely to respond to glucocorticoid treatment alone, but dexamethasone should provide symptomatic relief of selinexor-associated toxicity. In addition, dexamethasone may provide synergistic efficacy in combination with selinexor, which can reactivate glucocorticoid receptor (GCR) signaling. The current study will evaluate selinexor combined with dexamethasone for the treatment of MM in patients whose disease is refractory to previous treatment with a glucocorticoid, proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and the anti-CD38 monoclonal antibody (anti-CD38 mAb) daratumumab.

## 2. MULTIPLE MYELOMA

Multiple myeloma (MM) is a hematological malignancy characterized by the accumulation of monoclonal plasma cells in the bone marrow, the presence of monoclonal immunoglobulin, or M protein in the serum or urine, bone disease, kidney disease, and immunodeficiency. It is more common in elderly patients (median age at diagnosis is 65-70 years; only 2% of patients are younger than 40 years) ([Raab 2009](#)).

MM is the second most common hematological malignancy (after non-Hodgkin's lymphoma), representing 1% of all cancers and 2% of all cancer deaths. With current therapy, median survival is 5.2 years after diagnosis ([Kumar 2014](#)).

Although the cause of MM is unknown, a number of mutated genes have been found with significant frequency in patients with MM. These include mutations in NRAS, KRAS, TP53 and BRAF, which are well known oncogenic drivers for other cancers ([Lohr 2014](#)) and mutations in many genes associated with NF $\kappa$ B activation ([Keats 2007](#)). Also, certain risk factors make patients more susceptible to the disease. MM is more common in individuals over the age of 65, in males, and in those with family members affected by MM. Fifty percent (50%) of patients with MM harbor mutations in the immunoglobulin heavy-chain locus on chromosome 14q32, partial or complete loss of chromosome 13, and partial loss of chromosome 17 ([Raab 2009](#); [Kyle 2004](#)).

The diagnosis of MM is based on the key characteristics of the disease, occupation of the bone marrow cavity, the presence of space occupying bone lesions, and the production of paraprotein ([Raab 2009](#); [IMWG 2003](#)). The staging of MM is based on  $\beta_2$ -microglobulin level, which is directly correlated to renal function, tumor mass, and albumin level ([Greipp 2005](#)). The stages are summarized in [Appendix 2](#).

The treatment of MM has improved in the last 20 years due to the use of high-dose chemotherapy (i.e., alkylating agents) and autologous stem cell transplantation, the introduction of immunomodulatory agents, such as thalidomide, lenalidomide, and pomalidomide, and the proteasome inhibitors, bortezomib and carfilzomib. However, despite the increased effectiveness of these agents, most patients develop highly resistant MM and succumb to the disease. With over 12,500 deaths from MM expected in the USA in 2016 ([ACS 2016](#)), there remains a high unmet medical need to develop anti-MM agents with novel mechanisms.

### 3. NUCLEAR EXPORT

#### 3.1. Inhibition of XPO1 in Human Cancer

Many important tumor suppressing proteins (TSPs) have been identified in cancer pathogenesis, including but not limited to TP53, FOXO3a, IκB, BRCA1, APC, PP2A, and Rb ([Turner 2012](#); [Senapedis 2014](#); [Tan 2014](#); [Yang 2014](#)). TSPs mediate tumor suppression pathways via various functions including recognition of cellular damage, arrest of the cell cycle until repairs can be made, and induction of apoptosis in cells that are beyond repair ([Brown 2011](#)). Similarly, glucocorticoid binding to, and nuclear localization of, the GCR is required for its signaling.

The tumor suppression and anti-cancer activity of these TSPs and the GCR requires their presence in the nucleus. Conversely, export to the cytoplasm by nuclear export shuttle protein XPO1 can inactivate their abilities to regulate cellular processes ([Xu 2010](#)) and cancer cells exploit these functions to successfully evade normal DNA-damage controls as well as anti-neoplastic therapy. XPO1 is the only known nuclear export protein for the vast majority of TSPs and the GCR. Of note, XPO1 has been identified as a selective survival gene in MM by unbiased high-throughput short interfering ribonucleic acid (siRNA) screening ([Tiedemann 2012](#)) and is commonly overexpressed in MM ([Tai 2014](#)).

XPO1 blockade causes transient nuclear retention of TSPs, the GCR, and other growth modulators, re-establishing their tumor suppressing and growth regulating effects on cancer cells and potentially reversing mechanisms leading to chemotherapy resistance (which holds possible future implications for combination therapies) ([Lain 1999](#)).

Certain growth-promoting (including oncogene) messenger RNAs (mRNAs) require specialized nuclear export via a “cap-binding complex” in order to exit the nucleus into the cytoplasm where they are translated into proteins ([Culjkovic 2013](#); [Koehler 2007](#)). Several key MM genes including c-Myc, Cyclin D1, hDM2 and others utilize this complex via binding to the protein eIF4E in order to exit the nucleus and undergo efficient translation into protein. The cap-binding complex protein eIF4E is exported out of the nucleus into the cytoplasm exclusively by XPO1. As these proteins tend to have very short half-lives, constant translation is required to maintain their cellular levels. Inhibition of XPO1-mediated nuclear export leads to reduced translation of these growth-promoting proteins, and subsequently significant drops in their levels.

In normal cells, XPO1 inhibition transiently arrests the cell cycle without cytotoxicity followed by recovery after the inhibitor is removed ([Lain 1999](#); [van der Watt 2009](#); [Gray](#)

2007). Several attempts to develop this class of anti-cancer drug have failed due to off-target effects of the drugs which led to significant weight loss, diarrhea, and marked fatigue and asthenia in the early clinical trials ([Mutka 2009](#); [Newlands 1996](#); [Roberts 1986](#)).

It is now well recognized that forced nuclear retention of TSPs can counteract a multitude of oncogenic, growth stimulatory (and inflammatory) pathways that perpetuate the neoplastic phenotype. Similarly, nuclear retention of the GR in the presence of glucocorticoids could restore its activity. Finally, inhibition of eIF4E/XPO1-mediated mRNA export of oncoproteins lead to reductions in their levels. Because restoration of TSP ± GR activity and reduction in oncogenic signals are relevant to essentially any cancer, XPO1 inhibition is expected to have activity against MM and many other malignancies ([Table 2](#)).

**Table 2: Effect of XPO1 Inhibition on Oncogenic and Inflammatory Pathways**

Pathway Affected	Effect of XPO1 Inhibition	Reference
XPO1 overexpression	XPO1 reduction	<a href="#">Walker 2013</a>
Glucocorticoid Receptor (GR) Inactivation (nuclear export)	Nuclear GR retention (in presence of glucocorticoids) and reactivation	<a href="#">Chen 2014</a>
p53 mutation	p73 activation, p21 activation	<a href="#">Ranganathan 2012</a>
hDM2 (MDM2) activation	Nuclear p53 retention and activation, hDM2 protein reduction	<a href="#">Kojima 2013</a>
c-Myc amplification	MYC protein reduction	<a href="#">Schmidt 2013</a>
Cyclin D1 overexpression	Cyclin D1 reduction	<a href="#">Gao 2014</a>
NPM1 mutation	Restoration of nuclear NPM1	<a href="#">Falini 2007</a>
CEBPA down-regulation	Nuclear retention and activation	<a href="#">Ranganathan 2012</a>
CDKN2A reduction	p53/p73 stabilization	<a href="#">Azmi 2013</a>
Rb reduction	Rb hypophosphorylation, p14/p16 elevation	<a href="#">Fragomeni 2013</a>
FLT3 activation	FLT3 reduction	<a href="#">Ranganathan 2012</a>
c-KIT activation	c-KIT reduction	<a href="#">Ranganathan 2012</a>
NF-κB activation	IkB nuclear retention and activation	<a href="#">Lapalombella 2012</a>
PIK3 or AKT activation	FOXO1, -3, -4 activation	<a href="#">Lapalombella 2012</a>
Survivin – cytoplasmic	Survivin nuclear retention	<a href="#">Altura 2003</a>
Bcr-Abl activation	PP2A activation	<a href="#">Walker 2013</a>

## 4. SELINEXOR (KPT-330)

### 4.1. Introduction

Selinexor is an oral, first-in-class, slowly reversible, potent selective inhibitor of nuclear export (SINE) compound that specifically blocks exportin 1 (XPO1). XPO1 is responsible for the unidirectional export of ~220 different cargo proteins from the nucleus to the cytoplasm ([Xu et al., 2010](#)). The anti-neoplastic activity of SINE compounds is mediated

through at least three distinct pathways involving tumor suppressor proteins (TSPs), oncoproteins, and the glucocorticoid receptor. First, SINE compounds induce nuclear localization and functional activation of multiple TSPs, leading to rapid apoptosis of multiple myeloma (MM) ([Tai et al., 2014](#)) and other malignant cells. By forcing the nuclear localization and activation of TSPs, all cell types exposed to SINE compounds undergo G1 ± G2 cell cycle arrest, followed by a ‘genomic fidelity’ review. Cells with genomic damage (ie, malignant cells) are induced to undergo apoptosis both in vitro and in vivo. Normal cells, with an intact genome, remain in transient, reversible cell cycle arrest until the XPO1 block is relieved. A second anti-neoplastic effect of SINE compounds is mediated through the mRNA cap-binding protein eIF4E, which is also an XPO1 cargo. Amongst other functions, eIF4E is responsible for the efficient nuclear export and delivery of several growth-promoting (oncoprotein) mRNAs to cytoplasmic ribosomal for translation. By forcing the nuclear retention of the eIF43 bound to XPO1, SINE compounds reduce the cytoplasmic ribosomal synthesis of oncoprotein mRNAs including c-Myc, hDM2, Cyclin D1 and Bcl-XL. Finally, SINE compounds also lead to restoration of anti-myeloma glucocorticoid receptor (GR) signaling in the presence of glucocorticoids; selinexor and other SINE compounds do not appear to exacerbate the hyperglycemic effects of glucocorticoids. Thus, by inhibiting the key nuclear/cytoplasmic control protein XPO1, SINE compounds exhibit broad and deep anti-cancer activities.

## 4.2. Preclinical Data

In this section, a brief summary of preclinical data is provided. Additional information is presented in the current [Selinexor/KPT-330 Investigator’s Brochure](#).

*In vitro* experiments with continuous (~72 hour) exposure to selinexor demonstrated potent pro-apoptotic activity across a broad panel of tumor-derived cell lines and patient samples in culture, including multidrug-resistant cancers. Moreover, selinexor demonstrated cytotoxicity in MM and CLL cells in the absence or presence of bone marrow stroma cells (BMSC).

Pharmacokinetic (PK) studies were conducted in mice, rats and monkeys. Selinexor showed dose proportional exposure with no accumulation. Please see the current [Selinexor/KPT-330 Investigator’s Brochure](#) for more information.

Several studies were conducted to evaluate the effect of SINE compounds on MM *in vivo*. In MM1.S xenograft tumors, treatment with the SINE compound KPT-276 showed a marked decreased in tumor volume (40%) whereas tumor volume increased by 36% with placebo ([Schmidt 2013](#)). KPT-276 was also active in the Vk\*MYC mouse model of MM, which has a positive predictive value of 67% for the activity of single-agent compounds in clinical trials ([Schmidt 2013](#); [Chesi 2012](#)).

### 4.2.1. Selinexor plus Dexamethasone Combination Studies

*In vitro* studies showed selinexor and dexamethasone in combination were found to have a synergistic effect on reducing MM1.S human MM cell viability relative to either drug alone ([Chen 2014](#)). Increased GR nuclear localization and concomitantly activated GCR-mediated transcription in the presence of glucocorticoids were at least partly responsible for the synergistic cytotoxicity of this combination. ([Gao 2014](#)).



Enhanced activity of the selinexor plus dexamethasone combination was also observed in two xenograft models of human MM. The addition of dexamethasone to selinexor enhanced activity (86%) relative to selinexor alone.

In summary, the combination of selinexor and dexamethasone is synergistic *in vitro* and *in vivo* in MM cell cytotoxicity assays through increased nuclear localization of GCR and amplified GCR transcriptional activity. Taken together, these studies demonstrate that SINE compounds are active anti-MM compounds that cause decreased cell viability, increased apoptosis, and cell cycle arrest *in vitro* and potent inhibition of MM tumor growth *in vivo*, and that the addition of dexamethasone can augment these effects.

### **4.3. Clinical Experience**

As part of a Phase 1 clinical study of selinexor in patients with advanced hematological malignancies (KCP-330-001), 68 patients with MM that was relapsed and/or refractory to all available classes of approved therapies and was progressing on study entry received selinexor on a twice-weekly dose schedule. Preliminary results, as of 13 December 2016, are summarized below.

#### **4.3.1. Preliminary Results for Patients with MM, Study KCP-330-001, as of 13 December 2016**

##### **4.3.1.1. Preliminary Efficacy Results for Patients with MM, Study KCP-330-001**

###### **Selinexor plus Dexamethasone**

As of 13 December 2016, the best responses among the 22 evaluable patients who received selinexor plus dexamethasone (Sd) were: 1 CR (5%), 5 PRs (23%), 3 MRs (14%), 8 SDs (36%), and 5 PDs (23%). The ORR was 27% and the CBR was 41%. Several patients remained on study for >9 months and one patient remained on study for >1 year.

###### **Single-agent Selinexor**

Selinexor showed modest efficacy as a single-agent with 4% of patients achieving an objective response ( $\geq$ PR in 2 of 46 patients) and 26% showing clinical benefit ( $\geq$  MR in 12 of 46 patients). Overall, these preliminary Phase 1 results suggest that selinexor  $\pm$  dexamethasone has clear anti-MM activity in heavily pretreated patients.

##### **4.3.1.2. Preliminary Safety Results for Patients with MM, Study KCP-330-001**

Adverse events in patients receiving single-agent selinexor were generally low-grade, consistent with events observed in patients with other hematological malignancies and responsive to standard supportive care. Preliminary Results for Patients with MM, Study KCP-330-012, as of 01 December 2016

Preliminary efficacy and safety results from the first 79 patients were presented at the 2016 American Society of Hematology annual meeting and are summarized below ([Vogl et al., 2016](#)).

#### 4.3.1.3. Preliminary Efficacy (Response) Results for Patients with MM, Study KCP-330-012

Response rates in patients with MM previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and refractory to one proteasome inhibitor (PI), one immunomodulatory drug (Imid) and glucocorticoids (“quad” refractory) and in patients with MM refractory to the “quad” agents as well as to an anti-CD38 Ab (“penta” refractory) were adjudicated by an Independent Review Committee (IRC) and are presented in Table 3. for the first portion of the study overall, for 8 vs. 6 doses per 28-day cycle and “penta” vs. “quad” MM (Vogl et al., 2016). One patient did not have measurable myeloma at baseline and is not included in the efficacy analyses. The ORR across all patients is 21% and the clinical benefit rate (CBR) is 33%. Similar ORR were seen in the patients with “penta” and “quad” MM, with higher CBR in patients who received 8 vs. 6 doses/cycle consistent with improved disease control with continuous dosing. The additional 122 patients with “penta” MM to be added will receive 8 doses / cycle based on these analyses.

**Table 3: Response by Doses per Cycle and Prior Therapy Status as of 01 Dec 2016**

Category	N <sup>a</sup>	ORR (%)	CBR (%)	VGPR (%)	PR (%)	MR (%)	SD (%)	PD (%)	NE (%)
<b>Overall</b>	78	16 (21%)	26 (33%)	4 (5%)	12 (15%)	10 (13%)	27 (35%)	9 (12%)	16 (21%)
<b>8 doses/cycle</b>	27	6 (22%)	11 (41%)	1 (4%)	5 (19%)	5 (19%)	6 (22%)	5 (19%)	5 (19%)
<b>6 doses/cycle</b>	51	10 (20%)	15 (29%)	3 (6%)	7 (14%)	5 (10%)	21 (41%)	4 (8%)	11 (22%)
<b>Penta<sup>b</sup></b>	30	6 (20%)	12 (40%)	2 (7%)	4 (13%)	6 (20%)	6 (20%)	5 (17%)	7 (23%)
<b>Quad<sup>c</sup></b>	48	10 (21%)	14 (29%)	2 (4%)	8 (17%)	4 (8%)	21 (44%)	4 (8%)	9 (19%)

CBR=Clinical Benefit Rate (sCR+PR+MR), MR=Minor Response, NE=Non-Evaluable, ORR=Overall Response Rate (sCR+PR), PD=Progressive Disease, PR=Partial Response, SD=Stable Disease, VGPR=Very Good Partial Response

<sup>a</sup> one patient not included, did not have measurable myeloma at baseline

<sup>b</sup> the majority of these patients (19 of 30) received 8 doses per cycle

<sup>c</sup> the majority of these patients (40 of 48) received 6 doses per cycle

#### 4.3.1.4. Preliminary Safety Results for Patients with MM, Study KCP-330-012

Common treatment-related adverse events (TRAEs) based on a preliminary analysis of safety and tolerability (N=92; safety data cut off 31 March 2017):

- Hematological: thrombocytopenia (overall: 64%, Grades 3/4: 51%), neutropenia (overall: 26%, Grades  $\geq 3$  19%), and anemia (overall: 39%, Grade 3/4: 22%). There was one case of febrile neutropenia (1%) and one case of clinically significant bleeding related to thrombocytopenia (1%).



- Non-hematological: nausea (overall: 68%, Grade 3: 8%), fatigue (overall: 64%, Grade 3: 14%) anorexia (overall: 51%, Grade 3: 2%), vomiting (overall 41%, Grade 3: 2%), hyponatremia (overall 33%, Grade 3: 18%), diarrhea (overall 40%, Grade 3: 4%), and weight loss (overall: 33%, Grade 3: 1%).

These results are generally consistent with the overall TEAE results reported for all selinexor studies in patients with hematological malignancies (see the [Selinexor/KPT-330 IB](#)).

#### 4.3.1.5. Summary

Based on the promising preliminary efficacy results described above and on the considered feedback from MM experts that the population of patients with penta-refractory MM represents a current and growing high unmet medical need where there are no approved agents and there is no established standard of care, Karyopharm is expanding the number of patients with penta-refractory MM enrolled in this single-arm study to a total of ~160 patients with penta-refractory MM to receive Sd twice weekly for every week of each four-week cycle (8 doses/cycle).

#### 4.4. Potential Risks

Selinexor is currently in clinical development and has not been approved by the FDA for commercial use. Over 2,000 patients have received selinexor (as of 31 March 2017), however the entire safety profile is not known at this time. Measures will be taken to ensure the safety of the patients participating in this trial, including the use of stringent inclusion and exclusion criteria and close monitoring.

If toxicities are encountered, adjustments will be made to the study treatment as detailed in the sections that follow. All AEs and serious adverse events (SAEs) will be recorded during the trial and for up to 30 days after the last dose of study treatment or until the initiation of another anti-cancer therapy, whichever occurs first.

In ongoing clinical studies with selinexor, the most common AEs possibly related to selinexor are anorexia, fatigue, nausea, vomiting, diarrhea, and thrombocytopenia. Virtually all of these side effects can be managed effectively with dose modification and/or supportive care initiated prior to first dosing. Overall, the most frequently observed laboratory abnormalities include thrombocytopenia, hyponatremia, and a decrease in red blood cells. The majority of these have been mild to moderate. Please refer to the current [Selinexor/KPT-330 Investigator's Brochure](#) for more information.

Acute cerebellar syndrome (ACS) was reported at high doses in one adult (85 mg/m<sup>2</sup>) and two pediatric (70 mg/m<sup>2</sup>) patients in two phase 1 studies. The maximum doses in adults (70 mg/m<sup>2</sup>) and children (55 mg/m<sup>2</sup>) have been established largely based on these events. An adult patient, heavily pre-treated for recurrent pancreatic cancer, developed ACS following 3 doses of selinexor at 85 mg/m<sup>2</sup> twice weekly. The patient experienced abnormal speech, loss of coordination, and was unable to walk. Selinexor was discontinued and the patient's symptoms resolved to near baseline by ~6 weeks. A five-year old with refractory AML developed ACS following 4 doses of selinexor (70 mg/m<sup>2</sup>) followed by 5 days of fludarabine and cytarabine (without intrathecal therapy). The patient was empirically treated with intravenous immunoglobulin for 5 days, improved significantly over the next 3 weeks, and

had resolution of symptoms after 6 weeks. A repeat MRI 10 days after the initial image showed near complete resolution of diffusion abnormalities. A 19-month-old male (70 mg/m<sup>2</sup>) with relapsed AML developed ACS after receiving 4 doses of selinexor. Because the clinical and imaging findings were consistent with cerebellar toxicity, protocol therapy was discontinued and his ataxia showed improvement over the course of two weeks.

No other patients have reported such symptoms to date. All cases of cerebellar toxicity of Grade 3 or higher must be captured as an SAE and reported in an expedited Safety Report within 7 days of awareness of the event.

#### **4.4.1. Reproductive Risks**

Macroscopic and microscopic changes in reproductive organs were noted during rat and monkey toxicology studies; most resolved or partially resolved during the recovery period. The long-term effects of these changes on reproductive potential are unknown. Secondary developmental effects due to reduced maternal body weights were also noted during a study on rat embryo/fetal development. Please see the Selinexor (KPT-330) Investigator's Brochure for additional information. As it is unknown if selinexor produces any reproductive toxicity in humans, all patients must agree to use effective contraception (see Section 11.4.7) during the study and for 3 months after the end of treatment.

## **5. RATIONALE FOR THE STUDY**

Multiple myeloma is the second most common hematological malignancy. With conventional treatment methods, median survival is 5.2 years after diagnosis ([Kumar 2014](#)). Multiple myeloma is highly treatable but is not considered to be curable with currently available therapies. Common treatments include glucocorticoids, chemotherapy, proteasome inhibitors, immunomodulatory drugs, stem cell transplants, and radiation therapy.

Selinexor has demonstrated anti-MM activity in pre-clinical studies *in vitro* and *in vivo*. A summary of clinical results for 81 patients with MM seen in Study KCP-330-001, as of 01 August 2016, is provided in Section 4.3.

The original design of this protocol (KCP-330-012) was based on the primary treatment options for RR MM (i.e., IMiDs and PIs) that were in common use at the time that the protocol was developed, in order to evaluate whether selinexor would provide a useful, new therapeutic option to patients whose disease was RR to these treatments (i.e., patients with quad-refractory MM). In that design, a subset of patients with penta-refractory MM was also included as an exploratory endpoint, as treatment with anti-CD38 mAbs was not yet common. With the recent approval of daratumumab and ongoing development of isatuximab, the clinical use of anti-CD38 mAbs to treat RR MM has become more common, suggesting that selinexor would be best considered as a therapeutic option in patients with penta-refractory MM.

### **5.1. Rationale for Selinexor Dose Schedule**

More than 2,000 patients with advanced cancers have received selinexor in Phase 1 and Phase 2 studies as of 31 March 2017. In study KCP-330-001, patients who received selinexor

45 mg/m<sup>2</sup> (~80 mg) plus dexamethasone 20 mg, both dosed twice weekly, experienced durable response without clinically relevant cumulative toxicities. (See Section 4.3.)

Patients in the present study will receive selinexor 80 mg (45 mg/m<sup>2</sup> BSA) plus dexamethasone 20 mg, both dosed twice weekly, for each week of four-week cycles.

Dexamethasone 20 mg will be given with each dose of selinexor. For patients with partial intolerance to glucocorticoids (as determined by the Investigator) a minimum dose of dexamethasone 10 mg with each dose of selinexor is permitted. If any patient is not able to tolerate this dose, then a potential discontinuation or further decrease in dosage would be allowed after a discussion with the Medical Monitor on a case by case basis.

In select cases (e.g., for patients showing SD or PR and tolerating treatment particularly well), the selinexor dose may be increased by 20 mg to 100 mg, based on efficacy and safety considerations, after a minimum of two cycles of study therapy. However, in no case may the dose for any patient exceed 70 mg/m<sup>2</sup>. Prior to any potential dose increase, the BSA for the patient should be calculated. Patients with BSA < 1.4 m<sup>2</sup> may not have their dose increased, as this would result in a dose > 70 mg/m<sup>2</sup> selinexor.

## 6. STUDY OBJECTIVES

### 6.1. Primary Objectives

Evaluate the efficacy (overall response rate [ORR]) for treatment with selinexor 80 mg plus low-dose dexamethasone (20 mg) (Sd) twice weekly (four-week cycles) in patients with MM previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab; and refractory to prior treatment with glucocorticoids, an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and the anti-CD38 mAb daratumumab (herein referred to as “penta-refractory” MM).

ORR will include patients who experience partial response (PR), very good partial response (VGPR), complete response (CR), or stringent complete response (sCR), based on International Myeloma Working Group (IMWG) response criteria ([Kumar 2016](#)) for patients with penta-refractory MM in Part 2 (expansion phase).

### 6.2. Secondary Objectives

The following endpoints will be analyzed separately for (a) Part 1 patients with quad-refractory MM, (b) Part 1 patients with penta-refractory MM, and (c) Part 2 (expansion) patients with penta-refractory MM. Additionally, analyses of safety and tolerability will be performed on the overall population of patients from Parts 1 and 2 who received at least one dose of study treatment.

- Duration of response (DOR = Duration from first observation of at least PR to time of disease progression, or death due to disease progression, whichever occurs first. DOR will be censored for death due to any causes other than disease progression)

- Clinical Benefit Rate (CBR = sCR + CR + VGPR + PR + minimal response [MR]), and duration of clinical benefit (Duration from first observation of at least MR to time of disease progression or death due to disease progression, whichever occurs first. Duration of clinical benefit will be censored for death due to any causes other than disease progression.
- Disease Control Rate (DCR = CBR + stable disease [SD; for a minimum of 12 weeks])
- Progression Free Survival (PFS = Duration from start of study treatment to PD or death [regardless of cause], whichever comes first)
- Time to Progression (TTP = Duration from start of study treatment to time of disease progression) obtained with selinexor plus dexamethasone vs. TTP on most recent prior therapy
- Time to next treatment (TTNT)
- Overall Survival (OS = Duration from start of study treatment to death)
- Quality of Life (QoL) using the Functional Assessment of Cancer Therapy - Multiple Myeloma (FACT-MM)
- Safety and tolerability using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v 4.03.
- Describe the PK properties of selinexor in this patient population (Part 1 only)

### 6.3. Exploratory Objectives

The following endpoints will be analyzed separately for patients with penta-refractory MM and patients with quad-refractory MM:

- ORR, DOR, PFS, and OS in patients who were dosed with Sd for 4 weeks out of 4-week cycles (i.e., 8 doses per cycle) vs. patients who were dosed with selinexor for 3 weeks out of 4-week cycles (i.e., 6 doses per cycle)
- ORR and TTNT for Sd vs. the patient's last treatment regimen
- ORR, DOR, PFS, and OS in patients with Revised International Staging System (R-ISS) stage I vs. stage II vs. stage III)
- Minimal residual disease (MRD) in patients who achieve CR and sCR, and selected patients who achieve VGPR
- Correlational studies to evaluate response to treatment with selinexor as related to:
  - Cytogenetic and fluorescent in situ hybridization (FISH) prognostic markers, including p53 abnormalities and chromosomal aberrations (e.g., del 17p, t(4;14), t(14;16), del 13) and other MM cytogenetic classifications
  - R-ISS stage (I vs. II vs. III)
  - Time since initial diagnosis of active myeloma

- Lytic lesions as assessed by skeletal survey (or similar bone imaging)

## 7. STUDY DESIGN

### 7.1. Overview

This is a Phase 2b, single-arm, open-label, multicenter study of Sd (selinexor 80 mg plus dexamethasone 20 mg), both dosed twice weekly, four weeks of each four-week cycle, in patients with MM previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and the anti-CD38 mAb daratumumab. (Note: Refractory is defined as  $\leq 25\%$  response to therapy, progression during the previously described therapies, or progression within 60 days after completion of therapy.)

This study consists of two parts and will enroll approximately 210 patients overall. Part 1 (protocol V1.0-3.0) enrolled patients with both quad-refractory MM and penta-refractory MM. Part 2 (protocol V $\geq$ 4.0) will enroll patients with penta-refractory MM only, but continue all patients enrolled in Part 1.

The population for the primary efficacy analysis will contain only patients with penta-refractory MM enrolled in Part 2. Efficacy results for patients with quad-refractory MM and patients with penta-refractory MM enrolled in Part 1 will be analyzed separately. Safety analyses will be performed on the overall population of patients who received any amount of study treatment, presented overall and by study part, and separately for Part 1 penta-refractory MM patients and quad-refractory MM patients.

Patients will receive selinexor 80 mg (45 mg/m<sup>2</sup> BSA) plus dexamethasone 20 mg (Sd), both dosed twice weekly, for each week of four-week cycles. Patients will receive treatment until PD, death, toxicity that cannot be managed by standard care, or withdrawal, whichever occurs first.

Patients will also receive best supportive care to mitigate selinexor side effects, including blood product transfusions, antimicrobials, and (as appropriate) growth factors including granulocyte colony-stimulating factors for neutropenia, erythropoietins for anemia, and/or platelet-stimulating factors for thrombocytopenia.

In select cases (e.g., for patients showing SD or PR and tolerating treatment particularly well), the selinexor dose may be increased by 20 mg after consultation with the Medical Monitor. The dose level for an individual patient may be escalated based on efficacy considerations only after a minimum of 2 cycles of study therapy. However, in no case may the dose for any patient exceed 70 mg/m<sup>2</sup>. Prior to any potential dose increase, the body surface area (BSA) for the patient will be calculated and an individual patient's dose may not be increased if it would result in a dose  $> 70$  mg/m<sup>2</sup>.

In Part 2, MM-specific assessments (i.e., SPEP, UPEP, serum/urine immunofixation, quantitative Ig levels, serum FLC, and bone marrow aspirate) must be confirmed by a central laboratory to confirm CR or sCR, and select VGPR, per IMWG. Additional information is provided in the *Study Manual*.

The Investigator may remove a patient from study treatment using criteria described in Section 10.2. Patients may decide to discontinue study treatment for any reason. Patients who elect to discontinue study treatment should be encouraged to continue in the study so that follow-up information on disease progression, other antineoplastic therapy, symptoms and survival status may be obtained. However, patients may elect to withdraw consent and decline further participation in the trial at any time.

The Investigator must determine the primary reason for a patient's discontinuation of study treatment and record this information on the electronic case report form (eCRF). Patients who are prematurely withdrawn from study treatment are not eligible to re-initiate study treatment on this protocol at a later date.

## **7.2. Data Safety Monitoring Board**

An independent Data Safety Monitoring Board (DSMB) will review the safety of study treatment and any SAEs that occur during the study. Details on how the DSMB will review safety and response data are provided in the *DSMB Charter*.

The DSMB will be comprised of a minimum of two oncologists (at least one of whom specializes in hematologic oncology) and a statistician. Following their initial meeting, DSMB meetings will occur on a periodic basis in accordance with their charter.

## **7.3. Independent Review Committee**

An Independent Review Committee (IRC), will review disease assessment data to independently assess disease response. The IRC will review data that will be used for the analysis of the primary endpoint. The IRC's assessments of disease response and time to progression (TTP) will be used as the basis for the evaluation of the primary endpoint.

The IRC membership, functioning, and procedures (including resolution of any disagreements with Investigators regarding disease assessments) will be described in the *IRC Charter*.

## **7.4. Stopping Rules**

The entire study or treatment of individual patients may be stopped under defined circumstances as outlined in Section 10.

## **7.5. Study Endpoints**

Study objectives and endpoints are provided in Section 6.

## **7.6. Blinding and Randomization**

Not applicable; this is an open-label, single-arm, multicenter study.

## **7.7. End of Study**

The End of Study (EoS) will occur when all patients have completed the one-year Follow-up Period (i.e., when the last patient has expired, been followed for 12 months after last dose of study drug, been lost to follow-up, or has withdrawn consent, whichever occurs first).



## 8. SELECTION OF PATIENTS

### 8.1. Number of Patients

Approximately 210 patients will be enrolled overall, including ~160 patients with penta-refractory MM (Part 1 [~30] and Part 2 [~130]) and ~50 patients with quad-refractory MM (Part 1 only). See Section 7.1.

### 8.2. Recruitment

This study will be conducted at multiple sites in the United States and Europe.

### 8.3. Documentation Requirements

For enrollment consideration, patients may be eligible if they have *documented evidence* of previous treatment for MM that substantiates disease status as follows:

- Refractory to a glucocorticoid
- Refractory to lenalidomide and/or pomalidomide (only 1 required) *and* evidence of prior treatment\* with *both* lenalidomide and pomalidomide
- Refractory to bortezomib and/or carfilzomib (only 1 required) *and* evidence of prior treatment\* with *both* bortezomib and carfilzomib
- Refractory to daratumumab

\* Prior treatment is defined as either refractory, treatment with  $\geq 2$  cycles, or documented severe intolerance.

Documented evidence will include at least one of the following:

1. Medical records that support start and stop dates (month/year) of prior treatment (both dose and schedule), best response on prior treatment and, if applicable, date of progression (including both dose and schedule at the time of progression).
2. Myeloma marker values (SPEP, UPEP, Immunoglobulin, FLC) at the time of prior treatment start, stop and time of progression (accompanied by #1).
3. Formal, signed physician letter by Investigator (on hospital/clinic letterhead), to be included in the patient's medical and research record, indicating start/stop dates of prior treatment (both dose and schedule), best response on treatment and, if applicable, date of progression (including both dose and schedule at the time of progression).
4. Formal, signed physician letter from referring physician (on hospital/clinic letterhead), to be included in the patient's medical and research record, that includes prior treatment history indicating start/stop dates of prior treatment (both dose and schedule), best response on prior treatment and, if applicable, date of progression (including both dose and schedule at the time of progression).

## 8.4. Inclusion Criteria

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

1. Written informed consent in accordance with federal, local, and institutional guidelines.
2. Age  $\geq 18$  years at the time of signing informed consent.
3. Measurable MM based on IMWG guidelines as defined by at least one of the following:
  - a. Serum M-protein  $\geq 0.5$  g/dL by serum electrophoresis (SPEP) or, for IgA myeloma, by quantitative IgA
  - b. Urinary M-protein excretion  $\geq 200$  mg/24 hours
  - c. FLC  $\geq 100$  mg/L, provided that the FLC ratio is abnormal.
  - d. If serum protein electrophoresis is felt to be unreliable for routine M-protein measurement, then quantitative Ig levels by nephelometry is acceptable.
4. Patients must have previously received  $\geq 3$  anti-MM regimens including: an alkylating agent, lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab, and a glucocorticoid. There is no upper limit on the number of prior therapies provided that all other inclusion/exclusion criteria are met.
5. MM refractory to previous treatment with one or more glucocorticoids, parenteral PI (i.e., bortezomib and/or carfilzomib), IMiD (i.e., lenalidomide and/or pomalidomide), and daratumumab. Refractory is defined as  $\leq 25\%$  response to therapy, or progression during therapy or progression within 60 days after completion of therapy.
6. Multiple myeloma that is refractory to the patient's most recent anti-MM regimen. (Documented severe intolerance to the patient's last therapy is allowed upon approval by the Medical Monitor.)
7. Any clinically significant non-hematological toxicities (except for peripheral neuropathy as described in exclusion criterion #17) that patients experienced from treatments in previous clinical studies must have resolved to Grade  $\leq 2$  by Cycle 1 Day 1.
8. Adequate hepatic function within 21 days prior to Cycle 1 Day 1: total bilirubin  $< 2\times$  upper limit of normal (ULN) (except patients with Gilbert's syndrome who must have a total bilirubin of  $< 3\times$  ULN), AST  $< 2.5\times$  ULN and ALT  $< 2.5\times$  ULN.
9. Adequate renal function within 21 days prior to Cycle 1 Day 1: estimated creatinine clearance of  $\geq 20$  mL/min, calculated using the formula of Cockcroft and Gault.
10. Female patients of childbearing potential must agree to use 2 methods of contraception (including 1 highly effective and 1 effective method of contraception) and have a negative serum pregnancy test at Screening. Male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose of study treatment.



11. Eastern Cooperative Oncology Group (ECOG) Performance Status of  $\leq 2$ .
12. Adequate hematopoietic function within 21 days prior to Cycle 1 Day 1 (See Exclusion Criterion #20 for transfusion washout periods for RBCs and platelets):
  - a. Total WBC count  $> 1,000/\text{mm}^3$
  - b. ANC  $\geq 1000/\text{mm}^3$
  - c. Platelet count  $\geq 75,000/\text{mm}^3$  (patients in whom  $<50\%$  of bone marrow nucleated cells are plasma cells) or  $\geq 50,000/\text{mm}^3$  (patients in whom  $\geq 50\%$  of bone marrow nucleated cells are plasma cells. (Platelet transfusions  $< 1$  week prior to Cycle 1 Day 1 are prohibited [see below].)
13. Hemoglobin level  $\geq 8.5$  g/dL. In certain cases, patients with stable baseline hemoglobin level  $> 8.0$  may be included following approval by the Medical Monitor. (Red blood cell transfusions  $< 2$  weeks prior to Cycle 1 Day 1 are prohibited [see below].)
14. Confirmation of patient eligibility for specific key criteria for study participation with the Medical Monitor.

## 8.5. Exclusion Criteria

1. Active smoldering MM.
2. Active plasma cell leukemia.
3. Documented systemic amyloid light chain amyloidosis.
4. Active central nervous system (CNS) MM.
5. Pregnancy or breastfeeding.
6. Radiation, chemotherapy, or immunotherapy or any other anticancer therapy  $\leq 2$  weeks prior to Cycle 1 Day 1, and radio-immunotherapy 6 weeks prior to Cycle 1 Day 1.
7. Active graft vs. host disease (after allogeneic stem cell transplantation) at Cycle 1 Day 1
8. Life expectancy of  $< 4$  months.
9. Major surgery within four weeks prior to Cycle 1 Day 1.
10. Active, unstable cardiovascular function:
  - a. Symptomatic ischemia, or
  - b. Uncontrolled clinically-significant conduction abnormalities (e.g., patients with ventricular tachycardia on antiarrhythmics are excluded; patients with 1st degree atrioventricular (AV) block or asymptomatic left anterior fascicular block/right bundle branch block (LAFB/RBBB) will not be excluded), or
  - c. Congestive heart failure (CHF) of New York Heart Association (NYHA) Class  $\geq 3$ , or
  - d. Myocardial infarction (MI) within 3 months prior to Cycle 1 Day 1.
11. Active, uncontrolled hypertension.

12. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to first dose.
13. Known HIV seropositive.
14. Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface antigen).
15. Prior malignancy that required treatment, or has shown evidence of recurrence (except for non-melanoma skin cancer or adequately treated cervical carcinoma in situ) during the 5 years prior to enrollment. Cancer treated with curative intent > 5 years previously and without evidence of recurrence will be allowed.
16. Active GI dysfunction interfering with the ability to swallow tablets, or any GI dysfunction that could interfere with absorption of study treatment.
17. Grade  $\geq 3$  peripheral neuropathy, and Grade  $\geq 2$  painful neuropathy, within 21 days prior to Cycle 1 Day 1.
18. Serious, active psychiatric or medical conditions which, in the opinion of the Investigator, could interfere with treatment.
19. Participation in an investigational anti-cancer study within 21 days prior to Cycle 1 Day 1.
20. Receipt of transfusions as follows:
  - a. Platelet infusion within 1 week prior to Cycle 1 Day 1.
  - b. RBC transfusion within 2 weeks prior to Cycle 1 Day 1.
21. Receipt of the following blood growth factors within 2 weeks prior to Cycle 1 Day 1: Granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), erythropoietin (EPO), or megakaryocyte growth factor.
22. Known intolerance to or contraindications for glucocorticoid therapy at Cycle 1 Day 1.
23. Prior exposure to a SINE compound, including selinexor.
24. Unable or unwilling to comply with protocol requirements, including providing a 24-hour urine samples at the required study time points.

## **8.6. Screen Failures**

Patients who sign an informed consent form and do not receive study treatment for any reason are defined as screen failures. For all screen failures, the Investigator will enter the screening number, patient initials; and reason(s) for screen failure onto electronic case report forms (eCRFs). Screen failures will be replaced. Screen failures may be re-screened.

## **8.7. Study Patient Numbers**

Each patient will be assigned a unique study number and will keep this number for the duration of the study. Patient numbers will not be reassigned or reused for any reason.

Patients will be identified to the Sponsor only by their assigned number, initials, date of birth, and sex. The Investigator must maintain a patient identification master log.

## **8.8. Study Patient Number**

Each patient will be assigned a unique study number and will keep this number for the duration of the study. Patient numbers will not be reassigned or reused for any reason. Patients will be identified to Karyopharm only by their assigned number, initials, year of birth (as allowed by national and local regulatory authorities), and sex. The Investigator must maintain a patient identification master log.

## **9. METHODS OF ASSESSMENT AND ENDPOINTS**

### **9.1. Standard Study Assessments**

All assessments should be performed as outlined in [Table 1](#).

#### **9.1.1. Demographic Data**

During Screening, patient demographic data will be collected. These data include year of birth, age, gender, race, and ethnicity.

#### **9.1.2. Medical History**

A complete medical history will be obtained from each patient. Medical history includes historic MM assessment values (Day -30 and Day -60), baseline symptoms as well as a detailed history of prior procedures for MM and other prior cancer therapies (i.e., transplant, chemotherapy, hormonal therapy, immunotherapy, biotherapy, radiotherapy, and surgery) including start and stop dates, best response, disease progression dates (during or after therapy), as well as discontinuations due to intolerability or toxicity. Smoking history will be recorded. Data should be reviewed by the Investigator prior to dosing on Cycle 1 Day 1.

#### **9.1.3. Concomitant Medications**

Concomitant medications will be documented for each patient at each scheduled visit. A detailed history of medications will be documented in the eCRF. Subsequently, at each study visit, patients will be asked whether they have taken any medication other than the study medication (from Screening through the end of the study). All concomitant medications including dietary supplements, over-the-counter medications, and oral herbal preparations, as well as changes in medication, will be recorded on the eCRFs.

Supportive care (such as appetite stimulants, anti-emetics, and anti-diarrheals, etc.) is encouraged (see Section [11.4.2](#)).

#### **9.1.4. Physical Examination**

Full physical examinations (PE) during Screening and the EoT Visit will be performed. All other PEs during the study should be symptom-directed PEs. Significant findings that were present prior to the signing of informed consent must be included on the medical history page on the patient's CRF. Significant new findings, including the presence of plasmacytomas,

that begin or worsen after informed consent must be recorded on the Adverse Event or Plasmacytoma page of the patient's CRF.

PEs, unless otherwise noted, will include the following:

- Height (without shoes) in centimeters (cm) measured during Screening only
- Body weight (indoor clothing without shoes) in kilograms (kg)
- Body temperature
- Systolic and diastolic BP and pulse rate measured at each visit after the patient has been in a supine or sitting position for 5 minutes. BP should be assessed on the same arm at each visit.

Information about the PE must be present in the source documentation at the study site. Clinically relevant findings made after the start of selinexor plus dexamethasone dosing, which meet the definition of an AE, must be recorded on the AE eCRF.

#### **9.1.5. ECOG Score**

An ECOG Score Assessment (see [Appendix 1](#)) will be performed during Screening, Day 1 of each cycle, and the EoT visit.

### **9.2. Multiple Myeloma Disease Specific Assessments**

Patient response will be assessed by the procedures summarized in [Table 4](#) and graded according to the IMWG response criteria summarized in [Table 10 \(Appendix 3\)](#). Per IMWG, quantitative Ig levels by nephelometry may be used in place of SPEP for routine M-protein measurements for patients with IgA or IgD myeloma. Also, per IMWG, response may be confirmed if the patient fails to provide 24-hour urine sample collection after Screening activities occur. All MM assessments outlined in this protocol are required to be performed at each study visit, prior to dosing. If MM assessments are collected at unscheduled times, those results must be documented in the eCRF as unscheduled visits. This includes SPEP, UPEP, serum FLC,  $\beta_2$  microglobulin, quantitative Ig, and serum/urine protein immunofixation. Results of pre-screening MM assessments at Day -30 (window: Screening – 2 weeks) and Day -60 ( $\pm 15$  days) will also be provided.

SPEP with serum protein immunofixation, quantitative Ig, serum FLC, and 24-hour UPEP, with immunofixation, must be collected at each required time point. An aliquot of the blood and urine samples should be retained. If the local laboratory results indicate a CR or sCR, sequential MM disease assessment samples, per IMWG, will be collected. The sequential samples will be split – one aliquot of each sample will be sent to the local lab while the other aliquots, along with the initial assessment aliquots, will be sent to the central laboratory to confirm CR or sCR. If the results do not indicate CR or sCR, then the aliquots may be destroyed. Refer to the *Study Manual* for details.

All disease assessments (SPEP, UPEP, FLC, quantitative Ig, and serum/urine protein immunofixation) should be performed regardless of the diagnosis that is being followed (e.g., 24 hour UPEP collection must be collected at each time point outlined in the protocol even if the patient is being followed by SPEP, Ig or FLC).

**Table 4: Multiple Myeloma Disease-specific Assessments**

Procedure	Notes
SPEP with M-spike quantification, and serum protein immunofixation	Per IMWG.
UPEP (24-hour urine for total protein) with M-spike quantification and urine protein immunofixation	Per IMWG. If the patient fails to provide the 24-hour urine sample, this should be documented. All attempts should be made to collect the 24-hour urine sample at the required time points. UPEP must be determined from a urine sample collected for 24 hours – no other method is acceptable. UPEP must be performed at each time point outlined in the protocol even if the patient is being followed by SPEP.
Serum FLC	Per IMWG.
Quantitative Ig levels	Per IMWG. For IgA and IgD myelomas, quantitative immunoglobulin measurements are preferred for disease assessments; the same percentage changes apply as for serum M-spike. Only nephelometry can be used for the response assessment, and SPEP and nephelometric values cannot be used interchangeably ( <a href="#">Durie et al., 2006</a> ).
$\beta_2$ -microglobulin	For MM staging ( <a href="#">Appendix 2</a> ), not for assessing response
Skeletal survey	A skeletal survey (using x-rays and/or other clinically appropriate imaging modalities [MRI, whole body CT, or PET/CT]), as determined by the Investigator, will be performed within 45 days of C1 D1 and as clinically indicated, per Investigator discretion, during the study. The skeletal survey should include a lateral radiograph of skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. Results will be read by the local laboratory. If lytic bone lesions or plasmacytomas are observed at Screening, their number and size should be recorded in the CRF. Bone lesions and/or plasmacytomas seen at baseline should be re-assessed during the study at a frequency determined by the Investigator, using the same imaging modality that was used at Screening. <ul style="list-style-type: none"> <li>For patients without soft tissue plasmacytomas (i.e., bone lesions only), skeletal survey by X-rays or low-dose CT should be performed. Contrast is not required.</li> <li>For patients with soft tissue plasmacytomas, skeletal survey by X-rays or low-dose CT should be performed (contrast not required) and in addition MRI or CT or PET/CT, usually requiring contrast enhancement, should be performed.</li> </ul>
Clinical plasmacytoma	If plasmacytomas are detected at Screening by physical examination/palpation, they should be counted and measured per IMWG guidelines and recorded, and then reassessed and recorded during symptom directed physical examinations.
Bone marrow (BM) aspirate	The BM aspirate obtained at Screening will be used for (a) Karyotyping and FISH analysis (performed at a central laboratory) to confirm diagnosis and classify MM sub-type, and (b) separate non-tumor CD138– and tumor CD138+ cells for PDn, (c) exploratory MRD analysis on patients who achieve CR or sCR, and (d) high-risk

Procedure	Notes
	cytogenetic analysis. A central laboratory will be used for assessments b-d. Details for sample volumes can be found in the <i>Study Manual</i> .  A bone marrow core (trephine) biopsy may also be performed, as clinically indicated, to assess response.
Bone marrow core (trephine) biopsy	<i>Required:</i> To be performed as soon as possible after determination of CR and sCR based on serum and urine assessments (per IMWG).  A core biopsy is required when there is negative immunofixation of serum and urine, and disappearance of any soft tissue plasmacytomas to confirm response of CR and sCR.  <i>Optional:</i> Investigators may, at their discretion, choose to perform two optional bone marrow core biopsies (i.e., at Screening and after one cycle of treatment), <i>in addition</i> to required bone marrow aspirates or biopsies.  If sufficient sample is available, one portion of each biopsy should be fixed in 10% formalin and another portion from that same biopsy should be fresh frozen. An archival sample taken within 30 days prior to C1 D1 may be used in lieu of the pre-treatment sample. The post-treatment sample should be obtained after completing one full cycle on C2 D1 (+ 5 days) only from patients for whom a pre-treatment sample is also available.  These samples will be used for exploratory correlative PDn studies. Note: Patients must positively assent to these procedures on the ICF. These optional core biopsies may also be stored for up to 15 years for possible future correlative studies for genomic biomarkers.
FACT-MM	See Section <a href="#">9.9.2</a>

### 9.3. Multiple Myeloma Response Criteria

IMWG criteria ([Kumar 2016](#)) will be used in this study to assess response. All MM assessments are required at each time point as outlined in this protocol ([Table 1](#)).

Response will be assessed per IMWG response criteria for multiple myeloma ([Appendix 3](#)). Two consecutive samples are required to confirm the response. The time period between samples may be discussed with the Medical Monitor and can occur on the same day, as long as, the samples are analyzed separately.

- Complete response (CR)
- Stringent complete response (sCR)
- Very good partial response (VGPR)
- Partial response (PR)
- Minimal response (MR)
- Stable disease (SD)
- Progressive disease (PD)



## 9.4. Safety Assessments

Safety evaluations will be conducted at each visit and will include the procedures summarized below.

### 9.4.1. 12-Lead ECG

A standard 12-lead ECG will be performed as indicated in [Table 1](#). Patients must rest for at least 5 minutes prior to the ECG recording. The Investigator will interpret the ECG using one of the following categories: normal, abnormal but not clinically significant, or abnormal and clinically significant. The date and time the ECG was performed and the following parameters will be recorded in the eCRF: heart rate, PR interval, QT interval, QRS interval, and QT corrected (QTc) using Bazett's formula or calculated by the Fridericia correction formula ([Bazett 1920](#), [Fridericia 1920](#)). If Bazett correction is entered by the site, the Fridericia corrected QTc interval (QTcF) will be derived using the formula:  $QT/(RR^{1/3})$ , where  $RR = 60/\text{heart rate}$ .

### 9.4.2. Ophthalmic Exam

A full ophthalmic examination will be performed prior to the patient's first dose of selinexor. Prior to dilation, best corrected visual acuity (Snellen's Equivalent based on either Snellen chart or ETDRS chart), slit lamp examination including tonometry, following dilation, and funduscopy. If a cataract is seen during the examination, the cataract will be graded as follows:

- *Lens Opacities Classification System III (LOCS III)* – Patients who enrolled in this study under the original Protocol or Protocol Amendments 1 or 2 and had detectable cataracts graded according to the LOCS III will continue to have their cataracts graded according to LOCS III and will not switch to the new AOA Grade 1-4 cataract scale. For new patients or patients in whom no cataracts have been detected to date, if cataracts are detected, they will be graded according to the Grade 1-4 scale.
- *American Optometric Association (AOA) Cataract Grading System* – Starting with Protocol Amendment 3, new patients will be evaluated using the AOA grading system until they complete the study. This system is modified from the Optometric Clinical Practice Guideline: Care of the Adult Patient with Cataract, which is available on the AOA website ([www.aoa.org](http://www.aoa.org)) (See [Appendix 5](#).)

### 9.4.3. Clinical Laboratory Assessments

The following clinical laboratory tests should be performed as indicated in [Table 1](#).

- Hematology (blood sample: ethylenediaminetetraacetic acid [EDTA]) tests including hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count, WBC differential, red blood cell count, lymphocytes, monocytes, neutrophils, eosinophils, basophils, and platelets. WBC differential may be automated or manual as per institutional standards.

- Serum Chemistry (blood sample: serum)
  - Complete Serum Chemistry will include sodium, potassium, chloride, bicarbonate ( $\text{HCO}_3^-$ ), blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, LDH, total protein, albumin, amylase, lipase, creatine kinase and uric acid.
  - Limited Serum Chemistry will include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin and LDH, unless otherwise clinically indicated.
  - Thyroid-stimulating hormone (TSH)
- Coagulation parameters will include prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT).
- Urinalysis will include appearance, color, urine bilirubin, glucose, hemoglobin, ketones, pH, protein, specific gravity, and urobilinogen. Microscopy will only be performed if clinically indicated.

Blood chemistry will be analyzed at each study site by a certified local laboratory and a report of the laboratory values will be provided to the Investigator. The Investigator or designee will review the laboratory results and assess the clinical significance of all abnormal values. Appropriate action will be taken for any clinically significant abnormal values. Values will be documented on the laboratory report until stabilized, or the laboratory value returns to a clinically acceptable range (regardless of relationship to study medication) or baseline. Any laboratory value that remains abnormal at the EoT Visit and that is considered clinically significant will be followed according to accepted medical standards for up to 30 days or until resolution of the abnormality or return to baseline. Toxicity will be assessed using CTCAE version 4.03.

#### **9.4.4. Pregnancy Testing**

For females of childbearing potential, a negative serum human chorionic gonadotropin (hCG) pregnancy test must be obtained within 3 days before the first dose of study treatment. Test sensitivity for hCG must be  $\geq 25$  mIU/mL. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of Cycles  $\geq 2$  during the study and at the EoT Visit (serum hCG).

Pregnancy testing may also be performed as clinically indicated during the study.

### **9.5. Pharmacokinetic and Pharmacodynamic Procedures**

#### **9.5.1. Blood Sampling and Processing**

As of protocol version 5.0, these samples are no longer collected.

### **9.6. Pharmacokinetic Endpoints**

Pharmacokinetic analysis of selinexor plasma levels will be performed on blood samples from patients enrolled in Part 1 only. Pharmacokinetic endpoints to be evaluated include selinexor maximum plasma concentration and time-to-peak plasma concentration.



Plasma samples will be analyzed via a validated high performance liquid chromatography/tandem mass spectrometry (HPLC/MS-MS) method for plasma selinexor. Selinexor concentration data will be analyzed in a non-linear mixed effects population PK model with potential covariates including, but not limited to: age, body weight, gender, disease state, baseline hepatic or renal function, and concomitant medications. Measurements of selected plasma protein levels may be added as covariates in the PK analysis in order to investigate potential PK/PDn relationship. Details of the population PK analysis, including software, post-processing and statistical analysis, will be outlined in a separate Data Analysis Plan, to be completed prior to database lock.

## **9.7. Supportive and Exploratory studies**

Portions of the bone marrow aspirates and optional core biopsies will be used by the central lab to confirm response for patients who achieve CR and sCR and by Karyopharm for supportive efficacy and exploratory studies (analyses of cancer-related signaling molecules and pathways will be conducted by Karyopharm). Details of sample collection and processing can be found in the *Study Manual*.

### **9.7.1. Supportive Efficacy Endpoints**

Supportive efficacy (secondary and exploratory) endpoints for analysis are summarized in Section 6.2 and Section 6.3.

### **9.7.2. Pharmacodynamic Studies**

#### **9.7.2.1. Blood Samples for Plasma Proteins and Cytokines**

As of protocol version 5.0, these samples are no longer collected.

#### **9.7.2.2. Gene Expression Changes in RNA from Whole Blood**

As of protocol version 5.0, these samples are no longer collected.

#### **9.7.2.3. Bone Marrow Aspirates for PDn**

Twenty milliliters of bone marrow aspirate will be collected at Screening to isolate plasma, non-tumor CD138- and tumor CD138+ cell fractions for subsequent PDn studies. Studies may include transcriptomic, genomic and/or proteomic analyses to identify predictive biomarkers of selinexor response and to characterize the knowledge of selinexor MOA. In addition, tumor cells will be used to assess the presence of the high risk mutations including del(17p), t(14;16) and t(4;14) translocations. Cytogenetic analysis by karyotyping and FISH will be performed at a central laboratory to identify specific chromosomal translocations at sites known to show rearrangements in MM.

Aspirate samples containing patient DNA may be used for pharmacogenetic research to do the following:

- Study the causes of human diseases
- Help understand how different individuals respond to drugs
- Obtain information to help develop new methods to diagnose and treat diseases

The samples may be stored up to 15 years, depending on the laws of country where the study is conducted. The samples will be labeled with a code rather than with patient name or any other detail that could be used to identify the patient. These samples will be stored under the control of the Sponsor.

#### **9.7.2.4. Bone Marrow Aspirates for MRD Analysis**

An exploratory minimal residual disease (MRD) analysis may be performed on samples of bone marrow aspirates collected at the time of response in patients who achieve CR, sCR, or VGPR. Additional information about these procedures is provided in the *Study Manual*.

#### **9.7.2.5. Bone Marrow Core Biopsies Pre- and Post-treatment with Selinexor (Optional)**

Two optional bone marrow core (trephine) biopsies, (per Investigator's discretion) are requested for PDn exploratory studies. An archival sample taken within 30 days prior to C1 D1 may be used in lieu of the Screening (baseline) sample. The second sample should be obtained on C2 D1 (+5 days) only from patients for whom a baseline sample (including archival) is also available. If sufficient sample is obtained, one portion of each biopsy should be fixed in 10% formalin and another portion should be fresh frozen. Optional core biopsies may be stored for up to 15 years for possible future correlative studies for genomic biomarkers.

### **9.8. Efficacy Procedures**

#### **9.8.1. Objective Disease Assessment**

Procedures for confirming response are listed in [Table 4](#).

### **9.9. Efficacy Endpoints**

The primary efficacy objective/endpoints are provided in [Section 6.1](#); secondary efficacy endpoints are presented in [Section 6.2](#).

#### **9.9.1. Response Criteria**

Disease response will be assessed using IMWG ([Kumar 2016](#)). There is no maximum treatment duration. Disease response will be assessed centrally by an independent IRC ([Section 7.2](#)). Definitions of individual response criteria are provided in [Appendix 3](#).

#### **9.9.2. Quality of Life Assessment**

Health-related QoL and potential for improvement over the course of the study will be assessed by the FACT-MM patient-reported outcome questionnaire that is specifically relevant to MM. Additional information on the FACT-MM is provided in [Section 13.3.4](#).

Patients should complete the FACT-MM assessment *before* they undergo any study related procedure, including other study related evaluations, discussions with medical personal, physician and study treatment administration.

## **10. DISCONTINUATION CRITERIA**

### **10.1. Early Discontinuation of the Study**

The study may be discontinued at the sole discretion of the Sponsor for any reason, including medical or ethical reasons affecting the continued performance of the study, or difficulties in the recruitment of patients.

The DSMB will inform the sponsor if a safety signal is detected (see Section 7.2). The sponsor, in conjunction with appropriate regulatory authorities, would then decide if the trial should be modified or terminated. If this occurs, the sponsor will notify IRB/REB/ECs and investigators.

### **10.2. Early Discontinuation of Individual Patients**

The Investigator may remove a patient from study treatment at his/her discretion for any of the following reasons:

- Disease progression defined according to IMWG for progression of MM, including confirmatory analysis to document progression. Disease progression must be confirmed by the IRC prior to discontinuation of the study treatment
- Unacceptable AE(s) or failure to tolerate the study treatment
- Patient decides to discontinue study therapy
- Any medically appropriate reason or significant protocol violation, in the opinion of the Investigator

Reasons for discontinuation must be clearly documented in the source and in the study CRFs, including reasons for patient withdrawal and Investigator decision to discontinue the patient.

Patients may discontinue study treatment for any reason. Patients who elect to discontinue study treatment should be encouraged to continue in the study so that follow-up information on disease progression and survival status may be obtained. However, patients may elect to withdraw consent and decline further participation in the trial.

## **11. TREATMENT**

Selinexor study medication will be in the form of a coated, immediate-release tablet for oral administration. Selinexor tablets will be supplied as single-strength (20 mg) tablets in wallet-size blister packs. Dexamethasone 20 mg will be given with each dose of selinexor. Additional information is provided in Section 11.1.3.

### **11.1. Dosing and Administration**

#### **11.1.1. Dose Modifications**

All dosing modifications should be discussed with the study Medical Monitor prior to implementing the dosing change.

### **11.1.2. Labeling**

All drug containers will be labeled in accordance with current International Conference on Harmonization (ICH), GCP, and regulatory agency-specific requirements (e.g., FDA, MHRA). Medication labels will include the medication name, storage conditions, and batch number, and will comply with language and legal requirements of the US.

### **11.1.3. Dosing Information**

Selinexor will be administered as a fixed oral selinexor dose of 80 mg twice weekly (e.g., Monday and Wednesday or Tuesday and Thursday, etc.) on Weeks 1-4 of each four-week cycle. For doses on non-clinic days, the patient will be provided with doses by the hospital pharmacy to take home.

Dexamethasone 20 mg will be given with each dose of selinexor. For patients with partial intolerance to glucocorticoids (as determined by the Investigator), a minimum dose of 10 mg dexamethasone is permitted. If any patient is not able to tolerate this dose, then a potential discontinuation or further decrease in dosage would be allowed after a discussion with the Medical Monitor on a case by case basis. Dexamethasone will be provided to take home in the form of tablets.

In select cases (e.g., for patients showing SD, MR, or PR and tolerating treatment particularly well), the selinexor dose may be increased by 20 mg after discussion with the sponsor. The dose level for an individual patient may be escalated based on efficacy considerations after a minimum of 2 cycles of study therapy. However, in no case may the dose for any patient exceed 70 mg/m<sup>2</sup>. Prior to any potential dose increase, the BSA for the patient should be calculated. Patients may have their dose increased if it would result in a dose >70 mg/m<sup>2</sup>. For protocol versions < 5.0, blood sampling for PK and PDn correlative studies (as requested for Cycle 1 Day 1) will be repeated on the first day of dose escalation.

Selinexor should be given with, or within 30 minutes of, solid food consumption (to optimize tolerability) together with at least 120 mL (4 ounces) of fluids (water, juice, etc.) For details of drug formulation, preparation, and administration, please refer to [Appendix 4](#).

Selinexor tablets should be swallowed whole and should not be crushed to avoid increased risk of dermatologic toxicity if the powder comes in contact with skin.

Compliance to study treatment will be assessed by the Investigator or delegate at each patient visit and recorded in source documents after discussion with the patient and drug accountability. The date will be recorded as per study drug schedule. The Investigator or the designee will account for the number of tablets dispensed against those returned by the patient. Any deviations and missed doses will be recorded in the eCRF and drug accountability logs for verification with the reasons. The Investigator / designee will attempt to ensure complete compliance with the dosing schedule by providing timely instructions to the patients.

Patients may receive a study treatment holiday at any time during the four-week cycles, following prior consultation with the Medical Monitor.

#### **11.1.4. Dose Modifications for Patients with VGPR**

In an effort to improve long-term disease control and tolerability, this protocol allows for dose reductions in patients with very good anti-tumor activity of selinexor. Thus, for patients who achieve  $\geq$  VGPR for  $\geq$  6 months and who, in the opinion of the Investigator may benefit from dose reduction(s), the following modifications may be considered: (a) The dose of dexamethasone may be reduced by 40% or (b) the dose of selinexor may be reduced by 20 mg or (c) the frequency of selinexor may be reduced to once weekly, after consultation with the Medical Monitor. In general, dexamethasone should always be given on the day(s) of selinexor dosing. Patients whose doses are reduced under this schema should have appropriate MM markers monitored at least every two weeks (e.g., with FLC) so that dose may be re-escalated to their initial dose if evidence of progression occurs. These monitoring studies may be done at local laboratories.

#### **11.1.5. Dose Reduction Guidelines for Toxicity**

Toxicity will be graded according to CTCAE v.4.03 criteria; the therapy modifications described below are applied according to this severity grading.

If more than one type of toxicity occurs concurrently, the most severe grade will determine the modification.

Re-escalation of the study drug is allowed as outlined in the sections that apply for the specific toxicity. If drug-related toxicity requires a treatment delay of more than 28 days, the patient is taken off protocol treatment.

Each dose modification or treatment delay must be documented in the eCRF, including the respective reason.

Based on observations from the ongoing Phase 1 studies in patients with advanced hematological and solid tumors, selinexor shows a reasonably wide therapeutic range, with activities from  $\sim 6$  mg/m<sup>2</sup> to  $\geq 60$  mg/m<sup>2</sup>. Therefore, in order to optimize specific anti-tumor activity and the patient's tolerability, dose reductions and/or schedule modifications will be allowed as described in [Table 5](#) and [Table 6](#). Patients should also be treated aggressively with supportive care to reduce toxicities.

For all Grade  $\geq 3$  hematological or non-hematological AEs that are NOT selinexor related, after consultation with the Medical Monitor and at the discretion of the Investigator, selinexor dosing may be maintained, provided that the patient can continue to take the agent by mouth.

**Table 5: Pre-specified Dose/Schedule Modifications for Adverse Events Related to Study Drug**

	Dose Level	Selinexor Dosing
	1	100 mg BIW (total dose of 200 mg per week)
<b>Starting Dose</b>	<b>0</b>	<b>80 mg BIW (total of 160 mg per week)</b>
<b>Dose Reductions</b>	-1	60 mg BIW (120 mg total per week)
	-2	100 mg total per week: 100 mg one day OR divided as 60 mg and 40 mg on separate days
	-3	80 mg total per week: 80 mg one day OR divided as 40 mg per day on 2 days
	-4	60 mg total per week: 60 mg one day OR divided as 40 mg one day and 20 mg on another day
	-5	40 mg total per week: 40 mg one day OR divided as 20 mg per day on separate days

Abbreviation: BIW = twice weekly

**Table 6: Supportive Care and Dose Adjustment Guidelines**

**Please note the following recommendations:**

- After consultation with the Medical Monitor and at the discretion of the Investigator, selinexor dosing may be maintained for all hematological or non-hematological AEs that are NOT related to selinexor.
- For all selinexor-related AEs, if the prescribed dose reductions/interruptions in [Table 8](#) result in a stabilization of  $\geq 4$  weeks, a re-escalation may be considered after approval from the Medical Monitor.

Toxicity and Intensity	Selinexor Dose Modification
<b>Fatigue (common)</b>	
Grade 1 or Grade 2 lasting $\leq 7$ days	Maintain dose. Rule out other causes of fatigue, particularly dehydration and anemia. If found to be anemic, consider transfusing for hemoglobin $< 8$ g/dL. Institute supportive care medications per institutional guidelines and NCCN CPGO.  Patients with significant fatigue after several doses of selinexor may have an ongoing anti-tumor response. If fatigue is significant, consider assessment of tumor response as part of the patient's evaluation.
Grade 2 lasting $> 7$ days or Grade 3	Rule out other causes of fatigue, particularly dehydration and anemia. If found to be anemic, consider transfusing for hemoglobin $< 8$ g/dL. Institute supportive care medications per institutional guidelines and NCCN CPGO. Interrupt selinexor dosing until resolved to Grade 1 or baseline. For first occurrence, restart selinexor at current dose. For $\geq$ second occurrence, reduce selinexor by 1 dose level when resuming selinexor. ( <a href="#">Table 5</a> ).  Patients with significant fatigue after several doses of selinexor may have an ongoing anti-tumor response. If fatigue is significant, consider assessment of tumor response as part of the patient's evaluation.



<b>Toxicity and Intensity</b>	<b>Selinexor Dose Modification</b>
<b>Anorexia or Weight Loss</b>	
Grade 1 anorexia Grade 1 weight loss Grade 2 anorexia	Maintain dose. Rule out other causes and consider a repeat nutritional consultation and nutritional supplements (e.g., Ensure®, Boost®, etc.). Institute supportive care medications per institutional guidelines and NCCN CPGO.
Grade 2 weight loss Grade ≥ 3 anorexia or weight loss	Rule out other causes and consider a repeat nutritional consultation and nutritional supplements (e.g., Ensure®, Boost®, etc.). Institute supportive care medications per institutional guidelines and NCCN CPGO.  Interrupt dosing with selinexor until improves to Grade 1 or baseline and weight stabilizes, then reduce selinexor by 1 dose level when resuming selinexor (Table 5).  Consult Medical Monitor to discuss persistent or ≥ second occurrence of weight loss after stabilization.
<b>Nausea, Acute (common)</b>	
Grade 1 or 2 (If intolerable or persistent Grade 2 not responsive to supportive care, follow guidelines for Grade 3 below)	Maintain dose. Rule out other causes of nausea. Implement additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonists using institutional guidelines and NCCN CPGO.
Grade 3	Rule out other causes of nausea. Implement additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonists using institutional guidelines and NCCN CPGO.  Interrupt selinexor dosing until resolved to Grade ≤ 2 or baseline and restart selinexor at 1 dose level lower (Table 5).
<b>Hyponatremia (common)</b>	
Grade 1 (sodium levels < Normal to 130 mmol/L)	Maintain dose. Rule out other causes including drug (e.g., diuretic) effects. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose > 150 mg/dL).  Treat hyponatremia per institutional guidelines including dietary review. Consider addition of salt tablets to patient's diet.
Grade 3 with sodium levels 120 to <130 mmol/L without symptoms	Correct for hyperglycemia as outlined under Grade 1. Treat hyponatremia per institutional guidelines. If (corrected) sodium is Grade ≤ 3 and continues to be asymptomatic, then patient may continue current dosing provided that intravenous saline and/or salt tablets (1-3 times daily) are provided.  If Grade 3 is persistent or worsens or does not respond to treatment, hold selinexor until resolved to Grade 1 or baseline and reduce selinexor by 1 dose level.
Grade 3 with sodium levels 120 to <130 mmol/L with symptoms or Grade 4 (<120 mmol/L)	Correct for hyperglycemia as outlined under Grade 1. Treat hyponatremia per institutional guidelines. Delay/hold selinexor until resolved to Grade 1 or baseline then reduce selinexor dose by 1 level (Table 5).

Toxicity and Intensity	Selinexor Dose Modification
<b>Diarrhea (common)</b>	
Grade 1	Maintain selinexor dosing. Rule out other causes including drug effects. Initiate anti-diarrheal treatment per institutional guidelines.
Grade 2	Rule out other causes including drug effects. Treat per institutional guidelines. Interrupt selinexor until resolved to Grade 1 or baseline.  For first occurrence, restart selinexor at current dose. For $\geq$ second occurrence, reduce selinexor by 1 dose level (Table 5).
Grade 3 or 4	Delay selinexor until resolved to Grade 1 and the patient is clinically stable, then reduce selinexor dose by 1 dose level (Table 5).
<b>Thrombocytopenia</b>	
Grade 1 or 2	Maintain dose. Rule out other causes including drug effects.
Grade 3 Thrombocytopenia without bleeding	Consider platelet growth factors per institutional guidelines.  Do not interrupt/hold selinexor but dose reduce as below: For patients on 80 mg BIW (starting dose, Dose Level 0): Do not hold selinexor. Dose reduce to 100 mg total dose per week (Dose Level –2) but dosed at QW schedule until recovery to Grade $\leq$ 2 or baseline and then may resume the total weekly dose scheduled as BIW (100 mg divided as 60 mg and 40 mg).  For patients on all other dose levels: Do not hold selinexor. Dose reduce by one dose level but dose the patient at the total weekly dose as QW until further recovery to Grade $\leq$ 2 or baseline and then resume the total weekly dose scheduled as BIW. For example, patients who were on dose level –2 (100 mg QW or divided as 60 mg and 40 mg) and need to de-escalate to dose level –3 (80 mg total per week), should be dosed at 80 mg QW until platelets recover to Grade $\leq$ 2 or baseline and then may resume the same total weekly dose of 80 mg total as a divided schedule of 40 mg BIW.  *For $\geq$ second occurrence or worsening thrombocytopenia despite measures above: Hold selinexor until recovery to Grade $\leq$ 2 or baseline and resume at 1 dose level lower dosed at QW schedule.  In cases where there is significant disease involvement in the bone marrow (i.e., $\geq$ 50% marrow involvement) or pre-existing compromised marrow function (e.g., due to prior marrow-toxic therapy), the Investigator in consultation with the Medical Monitor may decide to continue selinexor dosing without dose reductions and/or interruptions as specified above, provided that platelet counts and bleeding symptoms/signs are closely monitored.



Toxicity and Intensity	Selinexor Dose Modification
Grade 4 Thrombocytopenia without bleeding	<p>Strongly consider platelet growth factors and transfuse per clinical practice/institutional guidelines.</p> <p>Delay or hold selinexor dosing until platelets recover to Grade <math>\leq 3</math> and see below:</p> <p>For patients on 80 mg BIW (starting dose, Dose Level 0): Hold selinexor until recovery to Grade <math>\leq 3</math>, then dose reduce to 100 mg total dose per week (Dose Level -2) but dosed at QW schedule until further recovery to Grade <math>\leq 2</math> or baseline and then may resume the total weekly dose scheduled as BIW (100 mg divided as 60 mg and 40 mg).</p> <p>For patients on all other dose levels: Hold selinexor until recovery to Grade <math>\leq 3</math>, then dose reduce by one dose level but dose the patient at the total weekly dose at the QW schedule until further recovery to Grade <math>\leq 2</math> or baseline and then may resume the total weekly dose scheduled as BIW. For example, patients who were on dose level -2 (100 mg QW or divided as 60 mg and 40 mg) and need to de-escalate to dose level -3 (80 mg total per week), should be dosed at 80 mg QW until platelets recover to Grade <math>\leq 2</math> or baseline and then may resume the same total weekly dose of 80 mg total as a divided schedule of 40 mg BIW.</p> <p>*For <math>\geq</math> second occurrence or worsening thrombocytopenia despite measures above: Hold selinexor until recovery to Grade <math>\leq 2</math> or baseline and resume at 1 dose level lower dosed at QW schedule.</p> <p>**If the occurrence falls on Day 1 of a cycle, delay the start of the cycle and check platelet counts weekly until recovery to Grade <math>\leq 3</math> and follow the guidelines above.</p> <p>In cases where there is significant disease involvement in the bone marrow (i.e., <math>\geq 50\%</math> marrow involvement) or pre-existing compromised marrow function (e.g., due to prior marrow-toxic therapy), the Investigator in consultation with the Medical Monitor may decide to continue selinexor dosing without dose reductions and/or interruptions as specified above, provided that platelet counts and bleeding symptoms/signs are closely monitored.</p>
Grade $\geq 3$ Thrombocytopenia with bleeding	<p>Delay/hold dosing until the bleeding has stopped and the patient is clinically stable. When resuming selinexor, see below:</p> <p>For patients on 80 mg BIW (starting dose, Dose Level 0): Upon recovery to Grade <math>\leq 2</math> or baseline, dose reduce to 100 mg total dose per week (Dose Level -2) but dosed at the QW schedule until further recovery to Grade <math>\leq 1</math> and then may resume the total weekly dose scheduled as BIW (100 mg divided as 60 mg and 40 mg).</p> <p>For patients on all other dose levels: Upon recovery to Grade <math>\leq 2</math> or baseline, dose reduce by one dose level, but dose the patient at the total weekly dose at the QW schedule until further recovery to Grade <math>\leq 1</math> or baseline and then may resume the total weekly dose scheduled as BIW.</p> <p>For example, patients who were on dose level -2 (100 mg QW or divided as 60 mg and 40 mg) and need to de-escalate to dose level -3 (80 mg total per week), should be dosed at 80 mg QW until platelets recover to Grade <math>\leq 1</math> or baseline and then may resume the same total weekly dose of 80 mg total as a divided schedule of 40 mg BIW.</p>

Toxicity and Intensity	Selinexor Dose Modification
	<p><b>**If the occurrence falls on Day 1 of a cycle, delay the start of the cycle and check platelet counts weekly until the bleeding has stopped, recovery to Grade <math>\leq 3</math> and the patient is clinically stable and follow the guidelines above.</b></p> <p>In cases where there is significant disease involvement in the bone marrow (i.e., <math>\geq 50\%</math> marrow involvement) or pre-existing compromised marrow function (e.g., due to prior marrow-toxic therapy), the Investigator in consultation with the Medical Monitor may decide to continue selinexor dosing without dose reductions and/or interruptions as specified above, provided that platelet counts and bleeding symptoms/signs are closely monitored.</p>
<b>Neutropenia</b>	
Grade 3 or 4 Neutropenia with fever (febrile neutropenia) or without fever	<p>Institute colony stimulating factors and prophylactic antibiotics as clinically indicated per institutional guidelines.</p> <p>Interrupt selinexor and check neutrophils weekly until recovery to Grade <math>\leq 2</math> or baseline and without fever (if febrile) and the patient is clinically stable. Reduce selinexor by 1 dose level when resuming.</p> <p>If the occurrence falls on Day 1 of a cycle, delay start of a cycle and check neutrophils weekly until recovery to Grade <math>\leq 2</math> or baseline and without fever (if febrile) and the patient is clinically stable. Reduce selinexor by 1 dose level when resuming.</p>
<b>Anemia</b>	
Treat per institutional guidelines including blood transfusions and/or erythropoietins. Consider transfusing for any hemoglobin $< 8$ g/dL. If possible, maintain selinexor dose as long as patient is clinically stable, but if dose reduction or interruption is desired, discuss with the Medical Monitor.	
<b>Other Selinexor-Related Adverse Events</b>	
Grade 1 or 2	Maintain dose. Rule out other causes. Initiate treatment and/or standard supportive care per institutional guidelines.
Grade 3 or 4	<p>Rule out other causes. Interrupt selinexor until recovery to Grade <math>\leq 2</math> or baseline and reduce selinexor by 1 dose level.</p> <p>Isolated values of Grade <math>\geq 3</math> alkaline phosphatase do NOT require dose interruption. Determination of liver versus bone etiology should be made, and evaluation of gamma-glutamyl transferase, 5'-nucleotidase, or other liver enzymes should be performed.</p>

Abbreviations: 5-HT3 = 5-hydroxytryptamine; BIW = twice weekly; NCCN CPGO = National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology; QW = once weekly

#### 11.1.5.1. Selinexor Dose Reduction for Decreased Glomerular Filtration Rate (GFR)

Selinexor is not significantly eliminated by the kidney; therefore, no dose alteration of selinexor is required with renal dysfunction. Creatinine clearance must be  $> 20$  mL/min in order to initiate therapy with Sd. If creatinine clearance declines during treatment and is believed to be unrelated to selinexor, the dose of selinexor may be maintained provided that the patient's condition is closely monitored. If creatinine clearances decline to  $< 20$  mL/min and this is felt to be related to selinexor, then the selinexor dose should be reduced by one level. If creatinine clearance returns to  $> 20$  mL/min for 4 weeks, then the dose of selinexor can be returned to previous level. If dialysis is implemented during Sd treatment, then Sd should always be given after dialysis.

#### **11.1.5.2. Selinexor Dose Adjustment in the Setting of Infection**

Patients with active uncontrolled or suspected infections should have Sd treatment withheld until the infection has clinically resolved or the patient is clinically stabilized.

Dexamethasone should be adjusted per institutional guidelines, and adrenal suppression considered. After the infection has resolved clinically, or the patient's clinical condition has stabilized, treatment with selinexor may continue at the original dose. Missed doses will not be replaced. Patients may continue on antibiotics or other anti-microbial agents for prolonged periods while re-initiating their selinexor regimen at the discretion of the Investigator.

#### **11.1.5.3. Conditions Not Requiring Selinexor Dose Reduction**

The following conditions are exceptions to the dose modification guidelines. Selinexor does not need to be held in the following cases:

- Alopecia of any grade
- Electrolyte or serum analyte (e.g., urate) abnormalities that are reversible with standard interventions

#### **11.1.5.4. Missed or Vomited Doses**

Note: A maximum of 2 doses of selinexor may be given per week.

##### **Missed Doses**

**If a dose was missed**, the schedule of that week should be altered to accommodate two doses in that week with at least 36 hours between two consecutive doses.

**If a dose must be skipped**, (e.g., due to recommendation of treating physician), the next dose will be taken as per schedule. Doses should not be administered less than 36 hours apart and all missed and delayed doses should be documented.

If a patient missed a full one or two-week period of dosing for non-study drug-related events (e.g., a required medical procedure or an unanticipated personal emergency), the days missed will be replaced. For example, if patient missed Cycle 2 Day 7 to Cycle 2 Day 14, then patient will start their next dosing on Cycle 2 Day 7 following the break. Similarly, if a patient misses Cycle 3 Day 1 to Cycle 3 Day 15, then the patient will start their next dosing on Cycle 3 Day 1. In this fashion, laboratory and radiographic assessments remain appropriate for timing of the administration of anti-cancer therapy.

##### **Vomited Doses**

If a dose is vomited  $\leq$  1 hour of ingestion, it will be replaced. If vomiting occurs  $>1$  hour after dosing, it will be considered a complete dose.

#### **11.1.5.5. Dose Escalation**

In select cases (e.g., for patients showing stable disease or partial response and tolerating treatment particularly well), the selinexor dose may be increased by 20 mg after discussion with the Medical Monitor. However, in no case may the dose for any patient exceed 70 mg/m<sup>2</sup>. Prior to any potential dose increase, the BSA for the patient should be calculated. For protocol versions  $< 5.0$ , blood sampling for PK and PDn correlative studies (as requested

for Cycle 1 Day 1) will be repeated on the first day of dose escalation. Patients will be followed as long as possible or until disease progression and death.

## **11.2. Study Drug Storage**

Selinexor tablets should be stored in a locked and secured area with access restricted to the site staff pharmacist or designee(s) at or below 86°F (30°C) (i.e., room or refrigerated temperature). Room temperature storage is preferred. The tablets should not be stored at freezer temperatures or frozen.

Selinexor tablets (20 mg) will be supplied in plastic film blisters with an aluminum foil lidding packaged in a secondary paper wallet with childproofing. See [Appendix 4](#) for detailed information on selinexor preparation, storage, stability, and administration.

Dexamethasone tablets should be stored as recommended on the product label.

## **11.3. Study Drug Accountability**

The Investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment (including lot/kit numbers) in a drug accountability log. Drug accountability will be noted by the clinical research associate (CRA) during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

As appropriate during the course of the study, and at study close out, the Investigator will return all used and unused study treatment and a copy of the completed drug accountability log to the CRA.

Selinexor should not be used for any purpose outside the scope of this protocol, nor can selinexor be transferred or licensed to any party not participating in the clinical study. Data for selinexor are confidential and proprietary and shall be maintained as such by the Investigators.

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of unused material.

All drug supplies provided by Karyopharm Therapeutics Inc. must be kept in an appropriate, limited access, secure place until used or returned to Karyopharm Therapeutics Inc. or designee for destruction. Drug supplies will be counted and reconciled at the site before being returned. The study site will be required to maintain a log of the temperature where the study medication is stored.

## **11.4. Concomitant Treatments**

### **11.4.1. Required 5-HT3 Antagonists**

In order to minimize nausea, unless contraindicated, all patients must receive 5-hydroxytryptamine (5-HT3) antagonists (ondansetron 8 mg or equivalent) starting before the first dose of selinexor and continued two or three times daily, as needed. Alternative anti-emetic agents may be used if the patient does not tolerate 5-HT3 antagonists.

#### **11.4.2. Supportive Care**

Supportive measures for optimal medical care should be provided during participation in this clinical trial. Based on clinical observations for 2103 adult patients evaluable for safety as of the 31 March 2017 safety data cutoff point, the main side effects associated with selinexor are primarily related to anorexia with poor caloric and fluid intake, fatigue, and nausea. Thrombocytopenia also occurs, although it is rarely associated with bleeding. In addition to dexamethasone included in the standard treatment plan, and required 5-HT3 prophylaxis (Section 11.4.1), supportive care including anti-nausea/anti-emetic therapy, acid suppression (proton pump inhibitors [PPI] and/or H2-blockers) and other treatments may be administered as described below:

- **Appetite stimulants:** megestrol acetate at a dose of 80-400 mg daily.
- **Centrally acting agents:** per National Comprehensive Cancer Network® [NCCN] Clinical Practice Guidelines® for antiemesis and anorexia/cachexia [palliative care])
- **Neurokinin 1 receptor antagonist (NK1R antagonist):** aprepitant or equivalent should be considered and will be covered for selected patients who have severe nausea and vomiting.

#### **11.4.3. Infection**

Appropriate broad-spectrum intravenous antibiotics and antifungal agents should be started immediately in patients who develop fever or other signs of systemic infection. Selinexor should be suspended in any patient with Grade 4 infection or clinical sepsis (in the absence of documented infection) until the condition is stabilized. Selinexor can then be re-started at the same dose.

##### **11.4.3.1. Other Glucocorticoid Side Effects**

The management of common glucocorticoid side effects is well documented. Aggressive use of proton-pump inhibitors (PPIs), anti-hypertensives and other agents is strongly encouraged in order to maintain the use of dexamethasone in combination with selinexor in this study.

Patients with documented osteopenia or osteoporosis should continue to take dexamethasone with selinexor as indicated in the study. Standard precautions such as use of bisphosphonates should be instituted unless contraindicated.

#### **11.4.4. Concomitant Medication and Treatment**

Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins, dietary supplements, over-the-counter medications, and oral herbal preparations. Patients may continue their baseline medication(s). All concomitant medication(s) must be reported in the eCRF. Any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s), and any clinical findings, if applicable.

#### 11.4.4.1. Permitted Concomitant Medication

Patients will receive concomitant medications to treat symptoms, AEs, and intercurrent illnesses that are medically necessary as standard care. Medications to treat concomitant diseases like diabetes, hypertension, etc., are allowed.

#### 11.4.5. Restricted Medications

*Medications:* Although acetaminophen (paracetamol) use in combination with selinexor was restricted in previous selinexor studies based on theoretical interactions with glutathione (GSH), ongoing clinical safety evaluations on the use of these drugs together have not shown any significant clinical or laboratory abnormalities with doses of acetaminophen up to 1 gram and selinexor up to 55 mg/m<sup>2</sup> (approximately 80-100 mg). Therefore, there are no longer any restrictions on the use of acetaminophen or acetaminophen-containing products in combination with selinexor, EXCEPT on days of selinexor dosing, when acetaminophen must not exceed a total daily dose of 1 gram.

*Diet:* There are no dietary restrictions on this study. Patients should maintain adequate caloric and fluid intake.

#### 11.4.6. Prohibited Medications

*Concurrent therapies:* Concurrent therapy with any non-study anticancer therapeutic is not allowed. Other investigational agents should not be used during the study. Use of any immunosuppressive agents during the study must be confirmed by the Medical Monitor.

*Medications:* Patients should not take glutathione (GSH)-, S-adenosylmethionine (SAM)-, or N-acetylcysteine (NAC)-containing products during this study as these products may enhance the metabolism of selinexor. Please see [Appendix 6](#) for a list of representative products. Patients must report all prescription and non-prescription medicines to their physicians during this study.

#### 11.4.7. Contraception Requirements

Patients should not become pregnant or father a child while on this study because the study treatments in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important that patients understand the need to use birth control while on this study. Female patients of childbearing potential must agree to use 2 methods of contraception (1 highly effective and 1 effective) and have a negative serum pregnancy test at Screening, and male patients must use an effective barrier method of contraception if sexually active with a female of childbearing potential.

Highly effective methods include:

1. Hormonal contraceptives (e.g., combined oral contraceptives, patch, vaginal ring, injectables, and implants)
2. Intrauterine device or intrauterine system



### 3. Vasectomy or tubal ligation

Effective methods include:

1. Barrier methods of contraception (e.g., male condom, female condom, cervical cap, diaphragm, and contraceptive sponge)

Of particular note,

- No barrier method by itself achieves a highly effective standard of contraception
- The proper use of diaphragm or cervical cap includes use of spermicide and is considered 1 barrier method.
- The cervical cap and contraceptive sponge are less effective in parous women.
- The use of spermicide alone is not considered a suitable barrier method for contraception.
- A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable (i.e., effective), but not highly effective, birth control methods.
- Male and female condoms should not be used together as they can tear or become damaged.

Alternatively, the following fulfill the contraception requirements:

1. A sexual partner who is permanently surgically sterilized or post-menopausal.
2. Total (true) abstinence (when this is in line with the preferred and usual lifestyle of the patient) is an acceptable method of contraception. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.

The methods of acceptable contraception must be explained to both male and female potential patients. In order to be eligible for the study, patients must agree to use the methods of birth control described above throughout the study and for 3 months following the last dose of study treatment at the time of consent for the study.

Please see Section 4.4.1 for additional safety information related to pregnancy.

#### **11.4.8. Radiation Treatment**

If clinically indicated, palliative radiation therapy to non-target lesions is permitted but study drug should be held for  $\geq 1$  day before the start of palliative radiation therapy and  $\geq 1$  day following each dose of palliative radiation therapy. Treatment with selinexor shall not be discontinued solely due to palliative radiation.

### **11.5. Treatment Compliance**

The Investigator or other study staff will supervise study drug treatment given in the clinic and instruct the patient on study medication self-administration.

Patients will be asked to bring their study medication container with them at each visit and compliance with protocol-defined study drug intake will be checked by pill count.

Compliance to study medication will be recorded by study personnel after discussion with the patient and drug accountability. Compliance to study medication will be assessed by the Investigator or delegate and recorded in source documents. The date will be recorded as per study drug schedule. The Investigator or the designee will account for the number of tablets dispensed against those returned by the patient. Any deviations and missed doses will be recorded in the eCRF and drug accountability logs for verification with the reasons.

The Investigator or designee will try to ensure complete compliance with the dosing schedule by providing timely instructions to the patients. In case of non-compliance, the patients will be instructed again.

## **12. ADVERSE EVENTS**

An AE is defined as any undesired medical occurrence in a patient or clinical investigation patient receiving a pharmaceutical product regardless of a causal relationship with this treatment. An AE can therefore be any unfavorable sign and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a study drug, whether or not related to the study drug.

Any treatment-emergent abnormal laboratory result or test result (e.g., PE, ECG, Echo, vitals, etc.), which is clinically significant, (i.e., meets one or more of the conditions listed below), should be recorded as a single diagnosis on the AE page in the eCRF:

1. Accompanied by clinical symptoms
2. Leading to a change in study medication (e.g., dose modification, interruption or permanent discontinuation)
3. Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

It is the responsibility of the Investigator to document all AEs that occur during the study. AE information will be elicited by asking the patient a non-leading 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 eCRF.

AEs should be reported for their actual grade and duration.

The term “severe” is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (e.g., ‘severe’ headache). This is not the same as “serious.” Seriousness of AEs is based on the outcome of an AE and usually associated with events that pose a threat to a patient’s life or functioning.

The severity of the AE will be graded according to the CTCAE Grading Scale (see the CTCAE web page at <http://ctep.cancer.gov> for details). For AEs not covered by CTCAE, the severity will be characterized as “mild,” “moderate,” or “severe” according to the following definitions:



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

The Investigator will make a judgment regarding the AE's relationship to study drug, as outlined below in [Table 7](#).

**Table 7: Classification of Adverse Events by Causality**

<b>Not related</b>	The lack of a temporal relationship of the event to study treatment makes a causal relationship not reasonably possible, or by any other drugs, therapeutic interventions or underlying conditions that provide a sufficient explanation.
<b>Related</b>	The temporal relationship of the event to study treatment makes a definitive relationship, and the event is more likely explained by exposure to the study treatment than by any other drugs, therapeutic interventions or underlying conditions.

## 12.1. Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that occurs at any dose (including after the ICF is signed and prior to dosing) that:

- Results in death
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- 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 on appropriate medical judgment, they may jeopardize the patient 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-patient 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.

Progression of the malignancy (including fatal outcomes) should not be reported as an SAE during the study or within the safety reporting period (see below). Sudden and unexplained death should be reported as an SAE.

#### **12.1.1. AE and SAE Follow-up**

All AEs occurring during the study are to be followed up in accordance with good medical practice until they are resolved, stabilized or judged no longer clinically significant or, if a chronic condition, until fully characterized. Any AEs that are considered drug-related must be followed until resolution or until stabilization.

#### **12.1.2. Post-Study Adverse Events and Serious Adverse Events**

All unresolved AEs should be followed by the Investigator until the events are resolved, the patient is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the Investigator should instruct each patient to report any subsequent event(s) that the patient, or the patient's personal physician, believes might reasonably be related to participation in this study.

Prior to the conclusion of the study at the site, the Investigator should notify the Karyopharm Pharmacovigilance Department (see Section 12.1.3.1) of any death or AE occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to this study.

After study conclusion, the Investigator should notify Karyopharm Therapeutics Inc., or its designee, of any death or AE he or she is aware of occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to this study. Karyopharm Therapeutics Inc. 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 patient that has participated in this study.

#### **12.1.3. Serious Adverse Event Reporting**

##### **12.1.3.1. Reporting Requirements**

ALL SAEs occurring in any patient, must be reported to the Karyopharm Pharmacovigilance Department within 24 hours of first knowledge of the event by the principal investigator or assigned site personnel. The following information will be requested from the investigational site:

- Protocol number
- Site and/or investigator number
- Patient number
- Demographic data
- Brief description of the event
- Onset date and time
- Resolution date and time, if the event resolved

- Current status, if event not yet resolved
- Any concomitant treatment and medication
- Investigator's assessment of the SAE's relationship to investigational product
- Outcome of the event, if available

This information will be captured in the SAE report form and/or the study specific safety database and will be forwarded to:

- Pharmacovigilance Department
- Karyopharm Therapeutics Inc.
- Email: [pharmacovigilance@karyopharm.com](mailto:pharmacovigilance@karyopharm.com)
- North American sites, Fax to US: +1-617-334-7617  
European sites, Fax to Germany: +49-89-9218-5650

Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with the FDA's "Safety Reporting Requirements for Investigational New Drugs and Bioanalytical/Bioequivalence Studies" or as per national regulatory requirements in participating countries.

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) or Ethics committee (EC), as applicable. Reporting of SAEs by the Investigator to the IRB or EC will be done in accordance with the standard operating procedures and policies of the IRB/EC. Adequate documentation must be maintained showing that the IRB/EC was properly notified.

In addition, Karyopharm Therapeutics Inc. will communicate all cases of cerebellar toxicities of Grade 3 or higher to the regulatory authority, IRBs and investigators, in the format of an expedited Safety Report within 7 days of awareness of the event.

## **12.2. Overdose**

An overdose is defined as a deliberate or accidental administration of study medication to a study patient at a dose above that which is assigned to that individual patient according to the study protocol. In the event of drug overdose, the Investigator and Karyopharm Medical Monitor should be notified immediately and the patient observed closely for AEs. The patient should be treated symptomatically as appropriate, and the incident of overdose and related AEs and/or treatment documented in the patient's medical record. In addition to documenting the overdose in the patient's records, the overdose must be reported to Karyopharm Pharmacovigilance on an SAE report form. Any AE or SAE observed as a consequence of the overdose will be handled as described in Section [12.2](#), as appropriate.

As selinexor is metabolized by GSH conjugation, it is conceivable that hepatic GSH depletion can occur in case of overdose. Therefore, in patients who develop liver function test abnormalities, supportive measures such as SAM 400 mg orally 1-4 times a day, or other drugs that can replace GSH, should be considered.

Medication errors, and uses of the study medication outside what is foreseen in the protocol, including misuse and abuse of the product must also be reported to Karyopharm Pharmacovigilance on an SAE report form.

### **12.3. Pregnancies**

Pregnancy *per se* is not considered an AE unless there is cause to believe that the investigational drug may have interfered with the effectiveness of a contraceptive medication.

Each pregnancy in a patient or partner of a patient on selinexor must be reported to the Sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Follow-up and documentation must occur even if the patient withdraws from the study or the study is completed.

The avoidance of fathering a child is recommended for 3 months following the discontinuation of selinexor therapy. No information is currently available regarding the effects of selinexor on fertility, gestation or subsequent child development.

Any pregnancy within 3 months post-study should be reported to the study investigator and the sponsor's designee.

## **13. STATISTICAL METHODS**

### **13.1. General Considerations**

#### **13.1.1. Statistical and Analytical Plans**

This is a Phase 2b, single-arm, open-label, multicenter study of selinexor 80 mg with dexamethasone 20 mg (Sd), both given orally twice weekly for each week of four-week cycles, to patients with MM previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and the anti-CD38 mAb daratumumab.

This study consists of two parts and will enroll approximately 210 patients overall. Part 1 (protocol V1-3) enrolled patients with both penta-refractory MM and quad-refractory MM. Part 2 (protocol V $\geq$ 4.0) will enroll patients with penta-refractory MM only, but continue all patients enrolled in Part 1.

The population for the primary efficacy analysis will contain only patients with penta-refractory MM enrolled in Part 2. Efficacy results for patients with quad-refractory MM and patients with penta-refractory MM enrolled in Part 1 will be analyzed separately. Safety analyses will be performed on the overall population of patients who received any amount of study treatment, presented overall and by study part, and separately for Part 1 penta-refractory MM patients and quad-refractory MM patients.

Hypothesis testing will be used for the primary efficacy endpoint data, in order to evaluate if selinexor plus dexamethasone provides statistically significant improvement in efficacy over a minimally acceptable level of 10% ORR. No formal hypothesis-testing will be used for other study data, such as demographics and safety data.

Tabulations will be produced for appropriate disposition, demographic, baseline, efficacy and safety parameters. For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented, as well as two-sided 95% confidence intervals (CI), unless otherwise stated. For continuous variables, the number of patients, mean, median, standard deviation (SD), minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier (KM) methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals, as well as percentage of censored observations.

### **13.1.2. Determination of Sample Size**

The sample size for this study addresses the primary study objective of evaluating the clinical effect of Sd in patients with penta-refractory MM by reference to a minimal threshold level for ORR, set to 0.10 (10%). Note that the original sample size estimation for the study in Part 1 was based on clinical assumptions for patients with quad-refractory MM, and the assumptions have been updated for patients with penta-refractory MM.

Based on preliminary evidence from an ongoing Phase 1 trial (KCP-330-001), it is believed that selinexor plus dexamethasone may exhibit substantial efficacy; therefore, the statistical test associated with the comparison to the threshold will maintain a Type I error rate of 0.025, one-sided.

For the primary efficacy analysis, a sample size of 122 patients with penta-refractory MM will allow a one-sided test at  $\alpha=0.025$  to detect an ORR of  $\geq 0.20$  against the threshold ORR of 0.10, with 90% power.

Overall, a total of ~210 patients will be enrolled, including ~130 newly enrolled patients with penta-refractory MM (Part 2; Versions  $\geq 4.0$ ) for the primary analysis and ~80 previously enrolled patients in Part 1 (~30 patients with penta-refractory MM and ~50 patients with quad-refractory MM enrolled under Versions  $<4.0$ ) for additional secondary and exploratory analyses.

### **13.1.3. Disposition of Patients**

A tabulation of patient disposition will be presented, including the number in each analysis population, the number with non-evaluable disease according to the IMWG criteria, the number censored at each of the PFS and OS analyses, the number lost to follow-up, the number that withdrew prior to completing the study, and reason(s) for withdrawal. This tabulation will be presented separately for each study part and by quad-refractory MM and penta-refractory patient populations in Part 1.

#### **13.1.4. Blinding and Randomization**

This is an open-label, single-arm study, therefore blinding and randomization are not applicable.

#### **13.1.5. Dose Adjustment**

The dose level for an individual patient may be escalated, based on efficacy considerations, after a minimum of 2 cycles of study therapy. Reasons for dose escalation can include, for example, a response of SD or PR with acceptable safety. Dose reduction can take place, based on the guidelines in Section 11.1.5. Additional exploratory analyses may be performed that investigate the impact of dose changes, should there be a sufficient number of dose adjustments.

### **13.2. Analysis Datasets**

#### **13.2.1. Populations to be Analyzed**

##### **13.2.1.1. Modified Intent-to-Treat (mITT) Population**

The modified intent-to-treat (mITT) population will consist of Part 2 patients with penta-refractory MM who met all eligibility criteria (or did not meet all eligibility criteria but received waiver from Sponsor to participate in the study), and received at least 1 dose of study treatment (partial or complete). This population will include patients who have discontinued therapy due to toxicity or disease progression and patients who have died from any cause, including those related to study drug or disease. This population (Part 2 patients with penta-refractory MM only) will be used for the primary analysis of efficacy.

##### **13.2.1.2. Per-Protocol Population**

A per-protocol (PP) population will consist of all patients in the mITT population who meet the following criteria:

- Have selinexor compliance  $\geq 70\%$ ,
- Have at least one adequate post-baseline response assessment unless died or withdrew from study before that.
- No major protocol violations that would compromise the assessment of efficacy. The list of major protocol violations that affect statistical analysis will be finalized before database lock.

Major violations will be determined independently of knowledge of response to therapy, prior to database lock and study analysis. This population will be used for supportive inferences concerning efficacy, however, if there are major differences between the results in this population and those obtained in the mITT population, this will be taken into consideration in the assessment of efficacy.

##### **13.2.1.3. Safety Population**

The safety population will consist of all patients who have received at least one dose of study treatment and have any post-baseline safety information.



#### **13.2.1.4. Sub-group Efficacy Analyses**

The subgroup comparisons of interest will be evaluated per the Statistical Analysis Plan (SAP) (version 1.0).

### **13.3. Data Analysis and Presentation**

Summary tabulations will be presented separately for each study part and by penta-refractory MM patients and quad-refractory MM patients in Part 1 for disposition as noted above, and for demographic, baseline, efficacy and safety data as noted in the following sections. All data collected on the eCRF will be provided in by-patient data listings.

#### **13.3.1. Demographic Characteristics**

Demographic characteristics will be summarized for the mITT, PP, and Safety populations and will include gender, race, ethnicity (Hispanic origin), and age at time of consent. For gender, race, and Hispanic origin, the summary statistics will be the number and percentage of patients within each category. The categories for race will be those recorded in the database. For age at time of consent, the mean, median, minimum, maximum, and standard deviation will be provided for each group and the total sample.

#### **13.3.2. Baseline Characteristics and Medical History**

Baseline characteristics include: performance status, duration from initial diagnosis, response to previous therapy, types of prior therapy, and height/weight. Baseline data will be tabulated using summary statistics for the mITT, PP, and Safety populations; no formal hypothesis testing will be performed.

Medical history and physical examination results at baseline will be tabulated for the same analysis populations.

#### **13.3.3. Primary Endpoint**

The primary statistical analysis of efficacy will be performed on ORR (achievement of PR, VGPR, CR or sCR) for the mITT population. For the primary analysis of superiority to the minimal threshold ORR, analysis will be performed using a two-sided 95% confidence interval, calculated for the rate of ORR, and statistical significance will be declared if the lower bound of this interval is greater than 10%.

#### **13.3.4. Secondary Endpoints**

The following secondary efficacy endpoints will be analyzed separately for mITT and PP populations.

- Duration of response (DOR = Duration from first observation of at least PR to time of disease progression [PD] or death due to disease progression, whichever occurs first. DOR will be censored for death due to any causes other than disease progression.
- Clinical Benefit Rate (CBR = sCR + CR + VGPR + PR + minimal response [MR]), and duration of clinical benefit (Duration from first observation of at least

MR to time of disease progression or death due to disease progression, whichever occurs first. Duration of clinical benefit will be censored for death due to any causes other than disease progression)

- Disease Control Rate (DCR = CBR + stable disease [SD; for a minimum of 12 weeks])
- Progression Free Survival (PFS = Duration from start of study treatment to PD or death [regardless of cause], whichever comes first)
- Time to Progression (TTP = Duration from start of study treatment to time of disease progression) obtained with selinexor plus dexamethasone vs. TTP on most recent prior therapy
- Time to Next Treatment (TTNT = Duration from start of study treatment to start of next anti-MM treatment or death due to disease progression, whichever occurs first)
- Overall Survival (OS = Duration from start of study treatment to death)
- Quality of Life (QoL) using the Functional Assessment of Cancer Therapy - Multiple Myeloma (FACT-MM)

Time-to-event endpoints (including duration of response, PFS, TTP, and OS) will be assessed using Kaplan-Meier (KM) methods, including an estimate of the median, as well as the 25<sup>th</sup> and 75<sup>th</sup> percentiles, along with two-sided 95% CIs. Duration of CBR will be regarded as descriptive adjuncts to the analyses of response rates. Clinical benefit (CBR) and disease control (DCR) rates will be statistically evaluated using two-sided 95% confidence intervals.

QoL will be assessed using the Functional Assessment of Cancer Therapy-Multiple Myeloma (FACT-MM). This instrument combines the General version of the FACT (FACT-G) with a MM-specific subscale (14 items). The subscales for the FACT-G are Physical Well-Being (7 items), Social/Family Well-Being (7 items), Emotional Well-Being (6 items), and Functional Well-Being (7 items). The trial outcomes index (TOI; total of 41 items) will be the primary measurement of interest, comprised of the Physical and Functional subscales plus the MM-specific subscale. Each item is rated on a 5-point Likert scale, ranging from 0 (“Not at all”) to 4 (“Very much”), therefore the TOI has a score ranging from 0 to 120. The QoL assessment will be performed at Baseline (prior to first dose of study treatment), Day 1 of each cycle on or after the second, and at the Final visit. The QoL analysis will be based on changes in the total TOI score from Baseline using paired T-tests. A secondary analysis of QoL will be performed in a similar manner using the total of all subscales. All 5 individual subscale total scores will be summarized over time using descriptive statistics.

Additionally, the following analyses of safety and tolerability secondary endpoints will be performed on the overall population of patients who received any amount of study treatment, presented overall and by study part.

- Safety and tolerability using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v 4.03.
- Describe the PK properties of selinexor in this patient population (Part 1 only).



### **13.3.5. Additional Exploratory Endpoints**

Supportive exploratory endpoint analyses will be performed using descriptive statistics, since such analyses are expected to be either supportive of the key efficacy endpoint results or hypothesis-generating and are not intended in this study to provide primary or confirmatory evidence of efficacy.

Several subgroup comparisons of interest will be evaluated as described in the SAP (version 1.0). Correlational analyses will be performed, to evaluate response to treatment with selinexor, may include the following:

- Cytogenetic and fluorescent in situ hybridization (FISH) prognostic markers, including p53 abnormalities and chromosomal aberrations (e.g., del 17p, t(4;14), t(14;16), del 13) and other MM cytogenetic classifications
- R-ISS stage (I vs. II vs. III)
- Time since initial diagnosis of active myeloma
- Lytic lesions as assessed by skeletal survey (or similar bone imaging)

### **13.3.6. Pharmacokinetic and Pharmacodynamic Data**

Plasma samples will be analyzed via a validated high performance liquid chromatography/tandem mass spectrometry (HPLC/MS-MS) method for plasma selinexor concentration. Selinexor concentration data will be analyzed for Part 1 patients only in a non-linear mixed effects population PK model with potential covariates including, but not limited to: age, body weight, gender, disease state, baseline hepatic or renal function, concomitant medications, and treatment. Measurements of selected plasma protein levels may be added as covariates in the PK analysis in order to investigate potential PK/PDn relationships. Details of the population PK analysis, including software, post-processing and statistical analysis, will be outlined in a separate PK/PDn Data Analysis Plan, to be completed prior to database lock. Results of these detailed PK and PK/PDn analyses may be presented in a separate report from, or appendix to, the primary clinical study report for this trial.

### **13.3.7. Safety Data**

Safety analyses will be performed on the overall population of patients who received any amount of study treatment, presented overall and by study part, and separately for Part 1 penta-refractory MM patients, Part 1 quad-refractory MM patients, and Part 2 penta-refractory MM patients. The original dose level for each patient will be used for safety analysis; no separate categories for dose escalation or reduction will be conducted in the primary analysis of safety. Additional exploratory evaluation of the impact of dose escalation or reduction on safety may be performed.

#### **13.3.7.1. Adverse Events**

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and displayed in tables and listings using MedDRA system organ class (SOC) and Preferred Term (PT).

Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined as any AE with onset, or worsening of a pre-existing condition, on or after the first dose of study treatment through 30 days following the last dose of study treatment, or any event considered drug-related by the Investigator through the end of the study. AEs with partial dates will be assessed using the available date information to determine if treatment-emergent; AEs with completely missing dates will be assumed to be treatment-emergent. No formal hypothesis-testing of AE incidence rates will be performed.

AEs will be summarized by patient incidence rates, therefore, in any tabulation, a patient contributes only once to the count for a given AE (preferred term). The number and percentage of patients with any treatment-emergent adverse events (TEAE) will be summarized for each treatment group, classified by SOC and preferred term. The number and percentage of patients with TEAEs assessed by the Investigator as at least possibly related to treatment will also be tabulated. The number and percentage of patients with any Grade  $\geq 3$  TEAE will be tabulated in the same manner.

The Investigator will judge the causal relationship between the occurrence of an AE and the study drug as not related, unlikely related, possibly related, or related. In the event a patient repeatedly experiences episodes of the same AE, then the event with the highest severity and/or strongest causal relationship to treatment will be used for purposes of tabulations.

All reported SAEs will be tabulated.

All AEs (treatment-emergent and post-treatment) will be listed in by-patient data listings, classified by treatment, patient and day on study. In addition, separate by-patient listings will be provided for the following: deaths; SAEs; and AEs leading to withdrawal.

#### **13.3.7.2. Laboratory Data**

Clinical laboratory values will be expressed using conventional units International System of Units (SI) units. The actual value and change from baseline (Day 1, prior to the first administration of study drug) to each on-study evaluation will be summarized for each clinical laboratory parameter, including hematology, clinical chemistry, coagulation and urinalysis. In the event of repeat values, the last non-missing value per study day/time will be used. In the event that Day 1 data are unavailable for a given patient/parameter, the Screening value will substitute as the baseline value.

Severity of select clinical lab measures will be determined using CTCAE v.4.03 criteria (e.g., those measures that have a corresponding CTCAE grade classification). Labs with CTCAE Grades  $\geq 3$  will be presented in a data listing. Shift tables that present changes from Baseline to worst on-study and Baseline to last on-study values relative to CTCAE classification ranges will be produced.

#### **13.3.7.3. Vital Signs, Physical Examinations, and ECOG Performance Status**

The actual value and change from baseline (Day 1) to each on-study evaluation will be summarized for vital signs. Shift tables that present changes from baseline to worst on-study and last on-study ECOG performance status values will be produced. By-patient listings of all vital sign measurements and ECOG performance status scores will be presented in data listings.

Physical examination results at Screening, and physical examination results changes during the study, will be summarized. All physical examination findings will be presented in by-patient data listings.

#### **13.3.7.4. Electrocardiogram Results**

Electrocardiogram results will be summarized descriptively, including heart rate and PR, QRS, QT, and QTc intervals (calculated by the Fridericia correction formula) intervals. If Bazett correction is entered by the site, the Fridericia corrected QTc interval (QTcF) will be derived using the formula:  $QT/(RR^{[1/3]})$ , where  $RR = 60/\text{heart rate}$ . Actual values and changes from baseline will be reported for each study visit.

Electrocardiogram data for each patient will be provided in a data listing.

#### **13.3.7.5. Ophthalmic Examinations**

Ophthalmic examination findings will be summarized descriptively by visit. All ophthalmic examination findings will be presented in the data listings.

#### **13.3.7.6. Concomitant Medications**

The use of concomitant medications will be included in by-patient data listings.

#### **13.3.8. Procedures for Handling Missing Data**

The procedures for handling missing data will be performed per the SAP (version 1.0).

### **13.4. Changes in the Conduct of the Study or Planned Analysis**

All deviations from the original statistical analysis plan will be documented and provided in the final clinical study report.

## **14. REGULATORY, ETHICAL AND LEGAL OBLIGATIONS**

### **14.1. Regulatory and Ethical Compliance**

This clinical study was designed, and shall be implemented and reported in accordance with, the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), Division 5 of the Health Canada Food and Drug Regulations - Drugs For Clinical Trials Involving Human Subjects, and with the ethical principles laid down in the Declaration of Helsinki.

### **14.2. Institutional Review Boards/Ethics Committees**

The protocol and the proposed informed consent form (ICF) must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and

procedures found in this protocol and to give access to all relevant data and records to Karyopharm, Quality Assurance representatives, designated agents of Karyopharm, IRBs/IECs/REBs and regulatory authorities as required.

### **14.3. Regulatory Authority Approval**

Before implementing this study, the protocol must be approved by the relevant, competent regulatory authority.

### **14.4. Protocol Adherence**

Investigators ascertain they will apply due diligence to avoid protocol deviations. All significant protocol deviations will be recorded and reported in the CSR.

### **14.5. Amendments to the Protocol**

Any change or addition to the protocol can only be made in a written protocol amendment that must be provided by Karyopharm, and approved by Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Karyopharm should be notified of this action and the IRB/IEC/REB at the study site should be informed according to local regulations (e.g., the UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

### **14.6. Informed Consent**

Eligible patients may only be included in the study after providing written consent (witnessed, where required by law or regulation) on an IRB/IEC/REB approved ICF.

Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a patient's informed consent was actually obtained will be captured in their eCRFs.

Karyopharm will provide to investigators, in a separate document, a proposed ICF that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Karyopharm or their designee must agree to any investigator suggested changes to this ICF before their submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Karyopharm or designee after IRB/IEC/REB approval. Additionally, consent will be requested to obtain/retain tissue samples (bone marrow biopsy) for future analysis as warranted by our rapidly-advancing understanding in this field. Each patient's informed consent document will reflect that samples collected may be used for pharmacogenomic investigations.

## **14.7. Patient Confidentiality and Disclosure**

The Investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Karyopharm or their designees. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

## **14.8. Collection, Auditing Study Documentation, and Data Storage**

### **14.8.1. Study Documentation, Record Keeping and Retention of Documents**

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. Each site will permit authorized representatives of the sponsor and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The study eCRF is the primary data collection instrument for the study. The Investigator should ensure the accuracy, completeness, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRFs, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. For electronic CRFs an audit trail will be maintained by the system.

The Investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

#### **14.8.2. Auditing Procedure**

In addition to the routine monitoring procedures, the Sponsor or the regulatory authority may conduct an audit or an inspection (during the study or after its completion) to evaluate compliance with the protocol and the principles of GCP.

The Investigator agrees that representatives of the Sponsor and Regulatory Authorities will have direct access, both during and after the course of this study, to audit and review all study-relevant medical records.

In the event that a major compliance or regulatory issues arises, the Sponsor may conduct an audit without prior warning.

#### **14.9. Disclosure of Information**

All information provided to the Investigator by Karyopharm, or their designee, will be kept strictly confidential. No disclosure shall be made except in accordance with a right of publication granted to the Investigator in the Clinical Trial Agreement.

No information about this study or its progress will be provided to anyone not involved in the study other than to Karyopharm, or its authorized representatives, or in confidence to the IRB, or similar committee, except if required by law.

#### **14.10. Discontinuation of the Study**

It is agreed that, for reasonable cause, either the Investigator or Karyopharm, may terminate the Investigator's participation in this study after submission of a written notice. Karyopharm may terminate the study at any time upon immediate notice for any reason including the Sponsor's belief that discontinuation of the study is necessary for the safety of patients.

#### **14.11. Reporting and Publication of Study Documentation**

Karyopharm assures that the key design elements of this protocol will be posted in a publicly accessible database such as [www.clinicaltrials.gov](http://www.clinicaltrials.gov). In addition, upon study completion and analysis of the resulting clinical data, the results of the study will be:

- Reported to appropriate, competent regulatory authorities in full compliance with International Conference on Harmonization (ICH) E3: Structure and Content of Clinical Study Reports. A primary clinical study report (CSR) may be written based on all available patient efficacy and safety data for the primary analysis; a final CSR may be submitted when all evaluable patients have completed the long-term follow up period, died, progressed, withdrawn consent, discontinued due to toxicity, or been lost to follow up. PK results may be reported in either CSR.
- Submitted for publication and/or posted in a publicly accessible database of clinical study results. Publication will be in a relevant peer-reviewed journal, with authorship status and ranking designated according to the acknowledged contributions of participating investigators, institutions and the Sponsor.

The results of PDn studies may be reported and/or published separately from the clinical study results.



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## APPENDIX 1. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS CRITERIA

**Table 8: Eastern Cooperative Oncology Group (ECOG) Performance Status Criteria**

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. 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	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649-655)

## APPENDIX 2. INTERNATIONAL STAGING SYSTEM FOR MULTIPLE MYELOMA

**Table 9: International Staging System for Multiple Myeloma**

Stage	Characteristics
Stage I	$\beta_2$ -microglobulin $<3.5$ mg/L, albumin $\geq 3.5$ g/dL
Stage II	$\beta_2$ -microglobulin $<3.5$ mg/L and albumin $<3.5$ g/dL, or $\beta_2$ -microglobulin 3.5-5.5 mg/L irrespective of the serum albumin
Stage III	$\beta_2$ -microglobulin $\geq 5.5$ mg/L

Source: Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. *J Clin Oncol*. 2005;23:3412-3420

### APPENDIX 3. INTERNATIONAL MYELOMA WORKING GROUP RESPONSE CRITERIA, MYELOMA

**Table 10: International Myeloma Working Group Response Criteria (Kumar 2016)**

Standard IMWG Response Criteria <sup>1,2,3</sup>	
Response Subcategory	Response Criteria
Complete response (CR)	Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas (SPDs), and < 5% plasma cells in bone marrow aspirates
Stringent complete response (sCR)	CR as defined above plus normal FLC ratio <sup>4</sup> and absence of clonal cells in bone marrow biopsy by immunohistochemistry ( $\kappa/\lambda$ ratio $\leq 4:1$ or $\geq 1:2$ for $\kappa$ and $\lambda$ patients, respectively, after counting $\geq 100$ plasma cells <sup>5</sup>
Very good partial response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or $\geq 90\%$ reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hr
Partial response (PR)	<p><math>\geq 50\%</math> reduction of serum M-protein plus reduction in 24-hr urinary M-protein by <math>\geq 90\%</math> or to &lt; 200 mg/24 hr.</p> <p>If the serum and urine M-protein are not measurable, a <math>\geq 50\%</math> decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria.</p> <p>If serum and urine M-protein and serum FLC assay are not measurable, <math>\geq 50\%</math> reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was <math>\geq 30\%</math>.</p> <p>In addition to the above criteria, if present at baseline, a <math>\geq 50\%</math> reduction in the size (SPD) of soft tissue plasmacytomas is also required.<sup>6</sup></p>
Minimal response (MR)	<p><math>\geq 25\%</math> but &lt; 49% reduction of serum M-protein and reduction in 24-hr urine M-protein by 50–89%.</p> <p>In addition to the above criteria, if present at baseline, a <math>\geq 50\%</math> reduction in the size (SPD) of soft tissue plasmacytomas is also required.<sup>6</sup></p>
Stable disease (SD)	Not recommended for use as an indicator of response; stability of disease is best described by providing the TTP estimates. Not meeting criteria for CR, VGPR, PR, MR, or PD.
Progressive disease (PD) <sup>7,8</sup>	<p>Any 1 or more of the following criteria:</p> <p>Increase of 25% from lowest confirmed response value in 1 or more of the following criteria:</p> <p>Serum M-protein with absolute increase of <math>\geq 0.5</math> g/dL;</p>

<b>Standard IMWG Response Criteria<sup>1,2,3</sup></b>	
<b>Response Subcategory</b>	<b>Response Criteria</b>
	<p>Serum M-protein increase <math>\geq 1</math> g/dL if the lowest M-component was <math>\geq 5</math> g/dL;</p> <p>Urine M-protein (absolute increase must be <math>\geq 200</math> mg/24 hr);</p> <p>In patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be <math>&gt; 10</math> mg/dL);</p> <p>In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels: bone marrow plasma cell percentage irrespective of baseline status (absolute increase must be <math>\geq 10\%</math>);</p> <p>Appearance of a new lesion(s), <math>\geq 50\%</math> increase from nadir in SPD<sup>6</sup> of <math>&gt; 1</math> lesion, or <math>\geq 50\%</math> increase in the longest diameter of a previous lesion <math>&gt; 1</math> cm in short axis;</p> <p><math>\geq 50\%</math> increase in circulating plasma cells (minimum of 200 cells per <math>\mu</math>L) if this is the only measure of disease</p>
Clinical relapse	<p>Clinical relapse requires 1 or more of the following criteria:</p> <p>Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of TTP or PFS but is listed as something that can be reported optionally or for use in clinical practice;</p> <p>Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression);</p> <p>Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a <math>50\%</math> (and <math>\geq 1</math> cm) increase as measured serially by the SPD<sup>6</sup> of the measurable lesion;</p> <p>Hypercalcaemia (<math>&gt; 11</math> mg/dL);</p> <p>Decrease in haemoglobin of <math>\geq 2</math> g/dL not related to therapy or other non-myeloma-related conditions;</p> <p>Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma;</p> <p>Hyperviscosity related to serum paraprotein</p>
Relapse from CR (to be used only if the endpoint is disease-free survival)	<p>Any 1 or more of the following criteria:</p> <p>Reappearance of serum or urine M-protein immunofixation or electrophoresis;</p> <p>Development of <math>\geq 5\%</math> plasma cells in the bone marrow;</p> <p>Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcaemia see above)</p>

<b>Standard IMWG Response Criteria<sup>1,2,3</sup></b>	
<b>Response Subcategory</b>	<b>Response Criteria</b>
Relapse from MRD negative (to be used only if the endpoint is disease-free survival)	Any 1 or more of the following criteria: Loss of MRD negative state (evidence of clonal plasma cell on NGF or NGS, or positive imaging study for recurrence of myeloma); Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of $\geq 5\%$ clonal plasma cells in the bone marrow; Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcaemia)

Abbreviations: ASCT = autologous stem-cell transplantation; CR = complete response; CRAB features = calcium elevation, renal failure, anemia, lytic bone lesions; CT = computed tomography; DOR = duration of response; FDG = fluorodeoxyglucose; FLC = free light chain; hr = hour; Ig = immunoglobulin; IMWG = International Myeloma Working Group; MM = multiple myeloma; MR = minimal response; MRD = minimal residual disease; MRI = magnetic resonance imaging; NGF = next-generation flow; NGS = next-generation sequencing; PD = progressive disease; PET = positron emission tomography; PFS = progression-free survival; PR = partial response; sCR = stringent complete response; SD = stable disease; SPD = sum of the products of the maximal perpendicular diameters of measured lesions; TTP = time to progression; VGPR = very good partial response.

Source: [Kumar, 2016](#)

<sup>1</sup> All response categories require 2 consecutive assessments made any time before starting any new therapy; for MRD there is no need for 2 consecutive assessments, but information on MRD after each treatment stage is recommended (e.g., after induction, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected CR. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported.

<sup>2</sup> Per IMWG, quantitative Ig levels by nephelometry may be used in place of SPEP for routine M-protein measurement for patients with IgA or IgD myeloma. Also, per IMWG, response may be confirmed if the patient fails to provide 24-hour urine sample collection after screening activities occur. See “Practical considerations for application of IMWG consensus criteria” section of the guidelines (page e340; Kumar, 2016).

<sup>3</sup> Derived from international uniform response criteria for MM ([Durie 2011](#)). MR definition and clarifications derived from Rajkumar ([Rajkumar 2011](#)). When the only method to measure disease is by serum FLC levels: CR can be defined as a normal FLC ratio of 0.26 to 1.65 in addition to the CR criteria listed previously. VGPR in such patients requires a  $\geq 90\%$  decrease in the difference between involved and uninvolved FLC levels. All response categories require 2 consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for SD, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as DOR.

<sup>4</sup> All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, United Kingdom).

<sup>5</sup> Presence/absence of clonal cells on immunohistochemistry is based upon the  $\kappa/\lambda$  ratio. An abnormal  $\kappa/\lambda$  ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is  $\kappa/\lambda$  of  $> 4:1$  or  $< 1:2$ .

- <sup>6</sup> Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.
- <sup>7</sup> Positive immunofixation alone in a patient previously classified as achieving a CR will not be considered progression. For purposes of calculating time to progression and PFS, patients who have achieved a CR and are MRD-negative should be evaluated using criteria listed for PD. Criteria for relapse from a CR or relapse from MRD should be used only when calculating disease-free survival.
- <sup>8</sup> In the case where a value is felt to be a spurious result per Investigator discretion (e.g., a possible laboratory error), that value will not be considered when determining the lowest value.

Questions regarding interpretation of these criteria may be addressed by consulting the, “Practical considerations for application of IMWG consensus criteria,” section of the guidelines (page e340, [Kumar 2016](#)).



## **APPENDIX 4. SELINEXOR FORMULATION AND ADMINISTRATION**

### **Description of Selinexor (KPT-330)**

Selinexor is a Selective Inhibitor of Nuclear Export (SINE) compound. Selinexor specifically blocks nuclear export by binding to the nuclear export protein XPO1.

*The chemical name is:* (Z)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)-N'-(pyrazin-2-yl)acrylohydrazide

*The molecular formula is:* C<sub>17</sub>H<sub>11</sub>F<sub>6</sub>N<sub>7</sub>O.

*The molecular weight is:* 443.31

### **Form**

Selinexor will be supplied and administered as 20 mg, coated, immediate-release tablets.

### **Storage and Stability**

Selinexor tablets (20 mg) will be supplied in plastic film blisters with an aluminum foil lidding packaged in a secondary paper wallet with childproofing. Selinexor should be stored in a locked and secured area with access restricted to the site staff pharmacist or designee(s), with temperature at or below 30°C (86°F). Room temperature storage is recommended, refrigerated is suitable. Tablets should not be stored frozen.

Selinexor tablets are currently in on-going stability studies. The expiry will be based on concurrent stability studies and extended during the course of the study as further stability data becomes available.

### **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

### **Availability**

Selinexor is an investigational agent and will be supplied free-of-charge from Karyopharm Therapeutics Inc.

### **Preparation**

No special preparation required.

NOTE: Tablets of selinexor should not be crushed because of increased risk of dermatologic toxicity if powder comes in contact with skin.

### **Administration**

Selinexor will be provided as tablets for oral administration. Selinexor is to be taken within 30 minutes of solid food consumption together with at least 120 mL (4 ounces) of fluids (water, milk, etc.).

Patients in the present study will receive selinexor 80 mg (45 mg/m<sup>2</sup> BSA) plus dexamethasone (20 mg), both twice weekly, during Weeks 1-4 of each four-week cycle.

### **Accountability**

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (see the Cancer Therapy Evaluation Program [CTEP] website at <http://ctep.cancer.gov/protocolDevelopment> for the “Policy and Guidelines for Accountability and Storage of Investigational Agents” or to obtain a copy of the drug accountability form).

### **Destruction and Return**

At the end of the study, unused supplies of selinexor should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

## APPENDIX 5. LENS OPACITIES CLASSIFICATION SYSTEM

For patients enrolled under protocol version 3.0, if a cataract is seen during the slit lamp examination to document lens clarity, the cataract will be graded according to the grading system shown below.

**Table 11: Lens Opacities Classification System**

<b>Grading of Cataracts*</b>				
<b>Cataract Type</b>	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
<b>Nuclear</b> Yellowing and sclerosis of the lens nucleus	Mild	Moderate	Pronounced	Severe
<b>Cortical</b> Measured as aggregate percentage of the intrapupillary space occupied by the opacity	Obscures 10% of intrapupillary space	Obscures 10% -50% of intra-pupillary space	Obscures 50% -90% of intra-pupillary space	Obscures >90% of intrapupillary space
<b>Posterior subcapsular</b> Measured as the aggregate percentage of the posterior capsular area occupied by the opacity	Obscures 10% of the area of the posterior capsule	Obscures 30% of the area of the posterior capsule	Obscures 50% of the area of the posterior capsule	Obscures >50% of the area of the posterior capsule
*Designation of cataract severity that falls between grade levels can be made by addition of a + sign (e.g., 1+, 2+). Grading of cataracts is usually done when pupil is dilated.				

Source: Optometric Clinical Practice Guideline: Care of the Adult Patient with Cataracts (CPG8). American Optometric Association at [www.aoa.org](http://www.aoa.org).

## APPENDIX 6. GLUTATHIONE (GSH)-, S-ADENOSYLMETHIONINE (SAM)-, OR N-ACETYLCYSTEINE (NAC)-CONTAINING PRODUCTS (REPRESENTATIVE LIST)

**Table 12: Glutathione (GSH)-, S-Adenosylmethionine (SAM)-, OR N-Acetylcysteine (NAC)-Containing Products (Representative List)**

Glutathione (GSH)		N-acetylcysteine (NAC)		S-adenosylmethionine (SAM)	
Product Name	Ingredient	Product Name	Ingredient	Product Name	Ingredient
Glutathione	glutathione	Antidote for acetaminophen overdose	acetylcysteine	SAM-e Complete	S-adenosyl-methionine
L-Glutathione	L-glutathione	Cerefolin NAC: medical food for age-related memory loss	L-methylfolate vitamin B12 N-acetyl cysteine	SAMe	S-adenosyl-L-methionine
Glutathione reduced	glutathione	NAC	N-acetyl cysteine	Double Strength SAMe 400	S-adenosyl-methionine
Reduced glutathione with alpha lipoic acid	Setria L-glutathione	N-A-C Sustain	N-acetyl L-cysteine		
Glutathione, Cysteine & C	glutathione L-cysteine vitamin C	Best NAC Detox Regulators	N-acetyl cysteine		
(Mega-) Liposomal Glutathione	glutathione				
Lypospheric GSH	glutathione				
Ivory Caps Skin Enhancement Formula	glutathione				

## APPENDIX 7. SUMMARY OF CHANGES

### Amendment 1

#### Amendment Rationale

The primary purpose for this amendment is to:

- Address the following FDA deficiency and comments provided in an e-mail message with the subject: “IND-114042 KPT-330-Deficiency and Comments”, dated: 21Jan2014:
  - Deficiency:
    - To be eligible for the trial, patients should have returned to  $\leq$  Grade 2 non hematological toxicities from previous treatment.
  - Comments:
    - The primary endpoint should be per central independent review committee including radiology review.
    - Time-to-event endpoints such as PFS/OS and Patient Reported Outcomes are not evaluable in non-controlled trials.

The revised protocol Version 2.0, dated 05Feb2015 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A summary of key changes that were made to protocol Version 1.0, including rationales for these changes, is provided below.

#### Changes to the Protocol

##### Administrative Changes

- Internal changes to improve clarity and eliminate inconsistencies between sections (**Modified sections:** Global)
- Updated the version number and date of protocol from Version 1.0 dated 15 Apr 2014 to Version 2.0 dated 05 Feb 2015 (**Modified sections:** Global)

##### Specific Content Changes

#### Synopsis

##### Table 1.1

- Changed the Screening Period from 14 days to 21 days prior to C1 D1
- Removed mention of randomization
- Added additional information in footnotes 22 and 23 for PK and PDn, respectively.

#### Section 7.2 Data Monitoring Committee

- Added sub-sections to clarify the roles of the DMC for reviewing safety and response data (the latter was added in response to comments by the FDA).

#### Section 8.3 Inclusion Criteria

- Added resolution of hematologic toxicities from previous treatments to  $\leq$  Grade 2 in response to a deficiency reported by the FDA

**Section 9.2.5 Survival Follow-Up**

- SPEP, UPEP and FLC every 3 months to assess durability of response was added to be consistent with the SOA

**Section 10.5 Skeletal Survey**

- Modified to include central read.

**Section 10.8 Pharmacokinetic Endpoints**

- Table 10.1 was revised to reflect PK and PDn blood and bone marrow (biopsy and aspirate) sampling

**Section 12.4 Concomitant Treatments**

- Redundant wording for restricted medications was deleted

**Section 14.3.4 Secondary Endpoints**

- Text was revised to clarify that PFS, QoL and OS will not be tested for statistical significance, in response to comments from the FDA.

## Amendment 2

### Amendment Rationale

The primary purposes for this amendment were to:

1. Revise the study target patient population from “quad-refractory” to “dual-refractory” as shown in the following modified inclusion criteria:

*From:* Patients must have “MM refractory to lenalidomide, pomalidomide, bortezomib, and carfilzomib.”

*To:* “Patients must have been previously exposed to lenalidomide, pomalidomide, bortezomib, and carfilzomib” *and have* “MM double refractory to previous treatment with both the PI and IMiD drug classes”

2. Change the study treatment (selinexor plus dexamethasone) dose schedule from “twice weekly for three weeks of every four-week cycle” to “twice weekly for every week of each four-week cycle.”

The revised protocol Version 3.0, dated 25 September 2015 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A summary of key changes that were made to protocol Version 2.0, including rationales for these changes, is provided below.

### Changes to the Protocol

#### Administrative Changes

- Revisions were made to harmonize procedures and assessments with those in clinical protocol KCP-330-017 (STOMP): A Phase 1b/2 Study of Selinexor (KPT-330) in Combination with Backbone Treatments for Resistant/Refractory Multiple Myeloma.
- Internal changes were made to improve clarity and eliminate inconsistencies across sections (**Modified sections:** Global)
- Updated the version number and date of protocol from Version 2.0 dated 05 February 2015 to Version 3.0 dated 25 September 2015 (**Modified sections:** Global)

#### Specific Content Changes

##### Title

*From:* A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) plus Low-Dose Dexamethasone in Patients with Multiple Myeloma Quad-refractory to Previous Therapies

*To:* A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) plus Dexamethasone in Patients with Multiple Myeloma Double-refractory to Previous Therapies

##### Indication

*From:* Multiple myeloma quad-refractory to prior treatment with bortezomib, carfilzomib, lenalidomide, and pomalidomide

*To:* Multiple myeloma refractory to prior treatment with an immunomodulatory agent (IMiD) and a proteasome inhibitor (PI)

## Synopsis

### Objectives

- Revised the Primary Objective for selinexor to be dosed four weeks (instead of three weeks) of each four-week cycle
- Moved the following objective from Exploratory Objectives to Secondary Objectives: “Determine ORR, DOR, PFS, and OS in the sub-group of patients with free light chain (FLC) MM”
- Revised objectives to state that patients must have been *exposed* to lenalidomide, pomalidomide, bortezomib, and carfilzomib, but their disease must only be shown to be refractory to the drug classes PIs and IMiDs (i.e., one drug in each class).
- Added minimal residual disease (MRD) assessment for patients who achieve sCR to Exploratory Objectives

### Background and Study Rationale

- Updated reported (preliminary) information on all four treatment groups in KCP-330-001 (i.e., selinexor  $\leq 30$  mg/m<sup>2</sup>, selinexor  $\geq 35$  mg/m<sup>2</sup>, selinexor 45 mg/m<sup>2</sup> + dexamethasone 20 mg, and selinexor 60 mg/m<sup>2</sup> + dexamethasone 20 mg) all as of 15 Dec 2014.

### Methodology

- Changed the selinexor plus dexamethasone dose schedule from “twice weekly for three weeks of every four-week cycle” to “twice weekly for four weeks of every four-week cycle.”

### Inclusion/Exclusion Criteria

- Revised to state that patients must have been *exposed* to lenalidomide, pomalidomide, bortezomib, and carfilzomib, but their disease must only be shown to be refractory to the drug classes PIs and IMiDs.

### Study Duration

- Added an End-of-Study definition: The study will end when all patients have completed the one-year Follow-up Period (i.e., when the last patient has expired, been followed for 12 months after last dose of study drug, been lost to follow-up, or has withdrawn consent, whichever occurs first).

### Criteria for Evaluation

- Changed the causality assessments  
*From:* 1) unrelated, 2) possibly related, or 3) related.  
*To:* 1) not related, 2) unlikely related, 3) possibly related, or 4) related.
- Added a list of the IMWG response criteria

### Table 1.1

- Reorganized the table for clarity and consistency of table, footnotes and Section 9 (Study Day Procedures), including:



- Added column for “Safety Follow-up Call”
- Added columns for “Cycle 2 Day 15” and “Cycles  $\geq 3$ ”
- Organized multiple study procedure rows under “Clinical Labs” and “Multiple Myeloma Specific Procedures”
- Revised wording for MM disease-specific assessments
- Revised study schedules for MM disease-specific assessments
- Added row for “Blood draws for PK analysis”
- Clarified requirements for when bone marrow aspirates are *required* and when optional bone marrow biopsies are *requested*.

### Section 1 Overview

- Updated overall selinexor clinical study information for > 1,000 patients who received selinexor as of 31 May 2015, as stated in the mostly recently issued Selinexor *Investigator’s Brochure*, version 5, released on 12 August 2015.

### Section 2 Multiple Myeloma

- Revised estimated mortality to 11,000 deaths anticipated due to MM in the US in 2015 as stated in <http://www.cancer.org/cancer/multiplemyeloma/detailedguide/multiple-myeloma-key-statistics>

### Section 4.3 Clinical Experience

- Provided additional summary information about preliminary results seen with selinexor and selinexor plus dexamethasone in the MM arm of the ongoing study KCP-330-001 (as of 01 Dec 2015), as presented in *Chen et al. ASH 2014*

### Section 5 Rationale for the Study

- Revised study target patient population from “quad-refractory” to “dual-refractory”

### Section 5.1 Rationale for Selinexor Dose Schedule

- Changed the study treatment dose schedule from “twice weekly for three weeks of every four-week cycle” to “twice weekly for four weeks of every four-week cycle.”

### Section 6.1 Primary Objective

- Revised study target patient population from “quad-refractory” to “dual-refractory”

### Section 6.2 Secondary Objectives

- Moved the following objective from Exploratory Objectives to Secondary Objectives: “Determine ORR, DOR, PFS, and OS in the sub-group of patients with free light chain (FLC) MM”
- Revised objectives to state that patients must have been *exposed* to lenalidomide, pomalidomide, bortezomib, and carfilzomib, but their disease must only be shown to be refractory to the drug classes PIs and IMiDs.

### Section 6.3 Exploratory Objectives

- Added minimal residual disease (MRD) assessment for patients who achieve CR or sCR to Exploratory Objectives

### **Section 7.1 Overview**

- Revised study summary to reflect the changes summarized above (i.e., dual-refractory target patient population and study treatment will be dosed for four weeks per four-week cycle)

### **Section 8.3 Inclusion Criteria**

- Changed:  
*From:* Patients must have “MM refractory to lenalidomide, pomalidomide, bortezomib, and carfilzomib.”  
*To:* “Patients must have been previously exposed to lenalidomide, pomalidomide, bortezomib, and carfilzomib” *and have* “MM double refractory to previous treatment with both the PI and IMiD drug classes”
- Added:  
Confirmation of patient eligibility for study participation with the Medical Monitor

### **Section 9 Study Plan and Procedures**

- Modified procedures and assessments to be consistent with Table 1.1 (Schedule of Assessments and Study Activities)
- Added a definition of End-of-Study (EoS): one year after the last patient to be enrolled has been treated for one year.

### **Section 10.2 Multiple Myeloma Disease Assessment**

- Added Table 6, a summary of the MM disease-specific assessments per IMWG guidelines

#### **Section 10.3.2**

- Revised ophthalmic exam to reference both LOCSIII (original protocol) and AOA (added in this amendment)

### **Section 10.5 Pharmacokinetic Endpoints**

- Revised Table 10.2 (Collection Time Points and Sample Volumes for PK and PDn) to include optional bone marrow core biopsies at Screening and Cycle 2 Day 1 (+ 5 days)

#### **Section 10.6.2 Pharmacodynamic Studies**

- Modified Section 10.6.2.3 (Bone Marrow Aspirates for FACS) for clarity
- Added Section 10.6.2.4 (Bone Marrow Aspirates for MRD Analysis) as new procedure
- Modified Section 10.6.2.5 (Bone Marrow Core Biopsies Pre- and Post-treatment with Selinexor [Optional]) for clarity

### **Section 12 Treatment**

- Table 12.2 (Dose Adjustment Guidelines for Selinexor) – removed dose adjustment guidelines for dexamethasone

### **Section 13 Adverse Events**

- Table 13.1 (Classification of Adverse Events by Causality) – Added a fourth option of “unlikely related” (to treatment with study drug)

### **Section 15.11 Reporting and Publication of Study Documentation**

- Revised to include options for reporting study results in more than one CSR

## Amendment 3

## Protocol Version 4

### Amendment Rationale

The primary purposes for this amendment were to:

1. Expand the population of patients with penta-refractory MM by enrolling approximately 130 additional patients. The overall study population is now ~210 patients.
2. Revise the study design to make the expansion population (Part 2) the mITT population for the primary efficacy analysis (using ORR); ORR for patients enrolled in Part 1 became a secondary analysis.

The revised protocol Version 4.0, dated 11 August 2016 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A summary of key changes that were made to protocol Version 3.0, including rationales for these changes, is provided below.

### Changes to the Protocol

#### *Administrative Changes*

- Revisions were made to simplify the protocol, including the elimination of repetitive references to schedules. (**Modified sections:** Global; Section 9 [in previous versions] was removed in its entirety)
- Added the abbreviation “Sd” to denote selinexor plus low-dose dexamethasone (i.e., selinexor [80 mg] plus dexamethasone [20 mg])
- Internal changes were made to improve clarity and eliminate inconsistencies across sections (**Modified sections:** Global)
- Updated the version number and date of protocol (**Modified sections:** Global)

#### *Specific Content Changes*

##### **Title**

*From:* A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) plus Dexamethasone in Patients with Multiple Myeloma Double-refractory to Previous Therapies

*To:* A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) Plus Low-Dose Dexamethasone (Sd) in Patients with Multiple Myeloma Previously Treated with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib, and an anti-CD38 Monoclonal Antibody (mAb) and Refractory to Prior Treatment with Glucocorticoids, an Immunomodulatory Agent, a Proteasome Inhibitor and an anti-CD38 mAb

## Indication

*From:* Multiple myeloma refractory to prior treatment with an immunomodulatory agent (IMiD) and a proteasome inhibitor (PI)

*To:* Multiple myeloma (MM) previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and an anti-CD38 monoclonal antibody (mAb) (i.e., daratumumab or isatuximab) and refractory to prior treatment with glucocorticoids, an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and an anti-CD38 mAb

## Synopsis

- Title and Indication as described above

## Objectives (also in Section 6)

- Revised to reflect the change to include the Part 2 expansion and the new primary objective/endpoint for ORR in penta-refractory patients enrolled in Part 2
- Added that the secondary objectives DOR, PFS, DCR, CBR, TTP and OS will be analyzed separately in different patient sub-populations (i.e., Part 1 patients with quad-refractory MM, Part 1 patients with penta-refractory MM, and Part 2 patients with penta-refractory MM).
- Added that the exploratory endpoints will be analyzed separately for patients with penta-refractory MM and patients with quad-refractory MM.
- Added the exploratory endpoint “ORR and DOR for Sd vs. the patient’s last treatment regimen” and “ORR, DOR, PFS, and OS in patients with International Staging System (ISS) state III vs. ISS stage I or II”.

## Rationale (also in Section 4.3)

- Added a summary of preliminary response results seen thus far in study KCP-330-001 and the current study (KCP-330-012)

## Methodology (also in Section 7.1)

- Added a brief description of Parts 1 and 2

## Inclusion/Exclusion Criteria (also in Sections 8.4 and 8.5)

- Merged inclusion criteria #3 with #4 to require measurable MM based on modified IMWG guidelines.
- Modified inclusion criteria #5 (now #4) to include either daratumumab or isatuximab
- Modified inclusion criteria #6 (now #5) to include patients with MM refractory to previous treatment with one or more glucocorticoids, parenteral PI (i.e., bortezomib in and/or carfilzomib), IMiD (i.e., lenalidomide and/or pomalidomide), and anti-CD38 mAb (i.e., either daratumumab or isatuximab).
- Modified inclusion criteria #7 (now #6) (multiple myeloma that is refractory to the patient’s most recent anti-MM regimen). The new wording in #6 states that “documented severe intolerance to the patient’s last therapy is allowed upon approval by the Medical Monitor.”

- Adjusted inclusion criterion #13 (now #12), requiring adequate platelet count of  $\geq 50,000/\text{mm}^3$  (patients in whom  $\geq 50\%$  of bone marrow nucleated cells are plasma cells) at baseline.
- Added inclusion criteria #13, regarding baseline hemoglobin level  $\geq 8.5$  g/dL.
- Deleted exclusion criteria #3, MM that does not express either M-protein or FLC is no longer excluded.
- Added exclusion criteria #20 and #21, also to require adequate hematopoietic function at baseline.
- Added exclusion criterion #22, to ensure that patients can tolerate dexamethasone.
- Added exclusion criterion #23, a standard item in protocols.

**Documentation Requirements** (also in Section 8.3)

- A formal statement was added to describe what documentation is needed to establish that patients are refractory to prior treatments.

**Study Numbers** (also in Section 13.1.2)

- Revised estimated enrollment for N=122 (for power analysis), and ~130 for enrollment.

**Study Duration:**

- Revised enrollment period from 15 months to 24 months.

**Statistical Methods** (also in Section 13)

- Re-stated the statistical assumptions underlying the revised primary endpoint.

**Table 1 (Schedule of Assessments)**

- Added FLC on C1D15 and C2D15
- Added emphasis that MM-specific lab assessments (i.e., SPEP, UPEP, FLC and quantitative Ig) must be performed at the time of PD to evaluate response. This is an essential requirement of the IMWG and was included in previous versions of this protocol, but its visibility is being increased in this version to support investigatory site staff.
- Reduced size of footnotes and added cross-referencing to protocol sections

**List of Abbreviations:**

- Deleted abbreviations that were not in use and added several new abbreviations

**Protocol, Main Body**

**Sections 7.2, 7.3 and 9.9.1**

- Establish an IRC to perform the central read of response data (for the efficacy analysis) that had been previously included under the Data Safety Monitoring Committee (DSMC) in previous versions of this protocol. The DSMC, now referred to as Data Safety Monitoring Board (DSMB) will retain its role of reviewing all study

safety data. Since this study may be pivotal for a regulatory submission, it is important that the involvement of an IRC was readily apparent.

## **Section 8.2**

- Added Canada and EU for potential investigatory sites.

## **Previous Section 9.1 – 9.2 (Study Plan and Procedures):**

- Deleted to improve overall protocol simplicity

## **Section 9.1:**

- Separated Physical Examinations and ECOG into separate sub-sections

## **Section 9.2:**

- Added confirmatory review of MM-specific assessments by central laboratory to confirm CR and sCR
- Added “modified” to IMWG and added citation of Palumbo 2014
- Table 5: Deleted column containing visit schedule for simplicity
- Added to UPEP that if the patient fails to provide the 24-hour urine sample, this should be documented. All attempts should be made to collect the 24-hour urine sample at the required time points.
- Changed confirmatory bone marrow sampling from aspirate to core biopsy.

## **Section 9.3**

- Added “modified” to IMWG and added citation of Palumbo 2014

## **Section 9.4.3:**

- Deleted several parameters (e.g., band neutrophils) that were not needed

## **Section 9.6**

- Revised section to indicate blood draws for PK analysis only required in Part 1

## **Section 10.2**

- Added that reasons for discontinuation must be clearly documented in the source and in the study CRFs, including reasons for patient withdrawal and Investigator decision to discontinue patient.

## **Section 11.1.5:**

- Modified Tables 7 and 8 to reflect our current understanding regarding how the selinexor dose should be modified in the presence of AEs during the study

## **Section 11.2 and Appendix 4:**

- Deleted selinexor 10 mg and 25 mg tablet strengths because they are not used in this study

**Section 11.4.5:**

- Moved Restricted Medications to this section from previous location in Section 9

**Section 11.4.6**

- Moved Prohibited Medications to this section from previous location in Section 9

**Section 12.2:**

- Moved “Overdose” to its own sub-section

**Section 13.2**

- Revised the definition of the mITT population for the primary efficacy analysis to include the statement “consist of Part 2 patients with penta-refractory MM who meet all eligibility criteria,” in addition to the existing definition of “who receive at least one dose of study treatment.”
- Updated the definition of the per-protocol (PP) population to encompass all patients in the mITT population who have completed at least one cycle of treatment and have no major protocol violations that would compromise the assessment of efficacy.
- Added Exploratory Efficacy Population that consists of all patients in Part 1 of the study who have received at least one dose of study treatment. Separate sub-group analyses will be conducted for quad-refractory and penta-refractory MM patients.

**Section 15:**

- Added Palumbo 2014 to the list of references

**Appendix 3:**

- Replaced IMWG Response Criteria from Kyle 2009 with comparable table from Palumbo 2014.



## Amendment 3.1

### Protocol Version 4.1

#### Amendment Rationale

The primary purpose for this amendment was to remove isatuximab as an allowable anti-CD38 agent for inclusion in the study. Per the FDA, it is not appropriate to include patients who have received isatuximab as the anti-CD38 agent for inclusion in the study because it is not approved at this time.

The revised protocol Version 4.1 (US-specific amendment), dated 06 February 2017 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A summary of key changes that were made to protocol Version 4.0, including rationales for these changes, is provided below.

#### Changes to the Protocol

##### *Administrative Changes (Modified Sections: Global)*

- Updated the version number and date of protocol
- Updated the number of patients who have received selinexor to the number based on the most recent Investigator's Brochure (14 November 2016)
- Replaced "minor" with "minimal" in regard to response
- Removed the qualifier "modified" from IMWG response criteria because the response criteria were updated to that based on [Kumar 2016](#)
- Internal changes to improve clarity

##### *Specific Content Changes*

##### **Title (Modified Sections: Global)**

*From:* A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) Plus Low-Dose Dexamethasone (Sd) in Patients with Multiple Myeloma Previously Treated with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib, and an anti-CD38 Monoclonal Antibody (mAb) and Refractory to Prior Treatment with Glucocorticoids, an Immunomodulatory Agent, a Proteasome Inhibitor and an anti-CD38 mAb

*To:* A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) Plus Low-Dose Dexamethasone (Sd) in Patients with Multiple Myeloma Previously Treated with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib, and Daratumumab, and Refractory to Prior Treatment with Glucocorticoids, an Immunomodulatory Agent, a Proteasome Inhibitor, and the anti-CD38 mAb Daratumumab

### **Indication (Modified Sections: Global)**

*From:* Multiple myeloma (MM) previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and an anti-CD38 monoclonal antibody (mAb) (i.e., daratumumab or isatuximab) and refractory to prior treatment with glucocorticoids, an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and an anti-CD38 mAb

*To:* Multiple myeloma (MM) previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and the anti-CD38 mAb daratumumab

### **Protocol Approval Signature Page**

- Replaced Michael Kauffman, MD, PhD, Acting Chief Medical Officer, with Humphrey Gardner, M.D., Senior Vice President, Clinical Development, as a signatory.

### **Inclusion/Exclusion Criteria (also in Sections 8.4 and 8.5)**

- Modified inclusion criteria #3d to remove turbidometry as an acceptable method to measure quantitative Ig levels.
- Modified inclusion criteria #4 and #5 to remove isatuximab due to FDA request
- Corrected inclusion criteria #7 to refer to exclusion criteria #17
- Corrected inclusion criteria #12 to refer to exclusion criteria #20
- Changed inclusion criteria #12a to total WBC count  $> 1,000/\text{mm}^3$  to update criteria for this patient population.
- Corrected exclusion criteria #17 to add  $\geq$  before Grade 2 painful neuropathy
- Modified exclusion criteria #22 to add or contraindication for before glucocorticoids to further clarify the medical intent of the original language.
- Added a new exclusion criterion immediately after exclusion criteria #22 and moved the previous #23 to #24. The addition of exclusion criteria #23, prior exposure to a SINE compound, including selinexor, provides consistency across Karyopharm protocols.

### **IMWG Response Criteria (also in Sections 6.1, 9.3, and Appendix 3)**

- Updated the IMWG response criteria for myeloma to align with the most recent IMWG criteria (Kumar, Lancet. 2016;17:328-346). The definition for MR was changed from “minor” to “minimal” response to align with the IMWG Consensus Criteria.

### **Documentation Requirements (also in Section 8.3)**

- Removed the requirement to show a patient was refractory to isatuximab to align with feedback on isatuximab from FDA.

### **Table 1 (Schedule of Assessments and also in Section 9.7.2.4)**

- Modified footnote #10 to remove text that scans and accompanying reports will be sent to the central laboratory to reflect current analytical procedures.
- Corrected footnote #12c to remove baseline collection of bone marrow aspirate for MRD analysis.

**List of Abbreviations:**

- Added the definitions for 5-HT3, ACS, and FLC (kappa/lamba ratio) for clarification

**Protocol, Main Body**

**Section 1**

- Updated text to reflect the current selinexor safety information.

**Section 4.4**

- Updated the information on ACS to include two pediatric patients to reflect the current selinexor safety information.

**Section 7.3 (also in Section 10.2)**

- Modified to require that an IRC confirm disease progression prior to a patient discontinuing study treatment to improve the consistency of clinical decisions across the sites.

**Sections 9.2 (also in Appendix 3)**

- Revised the modifications to the IMWG response criteria modified to allow for quantitative Ig levels by nephelometry to be used in place of SPEP for routine M-protein measurements for patients with IgA or IgD myeloma.

**Table 5**

- Updated text to clarify UPEP, serum FLC, Quantitative Ig levels, Skeletal survey, and Clinical plasmacytoma assessments.
- Removed the following text for skeletal survey to reflect current analytical procedures: “the scans and accompanying radiology reports will be sent to a central lab. Details regarding the central lab procedures including collection and shipment of data will be described in the Study Manual.”

**Section 9.4.1 (also in Section 15)**

- Modified to include the Fridericia correction formula for consistency within the protocol and added references for Bazett’s and Fridericia’s formulas.

**Table 6**

- Added footnote #5 to PDn Predictive Biomarkers, “Sample will not be collected by European sites,” due lack of feasibility of shipping from EU sites to US testing facility.

**Table 8**

- Added the following text above the table to reflect current guidance: Please note the following recommendations: After consultation with the Medical Monitor and at the

discretion of the Investigator, selinexor dosing may be maintained for all hematological or non-hematological AEs that are NOT related to selinexor. For all selinexor-related AEs, if the prescribed dose reductions/interruptions in Table 8 result in a stabilization of  $\geq 4$  weeks, a re-escalation may be considered after approval from the Medical Monitor.

- Updated text throughout table to reflect the most recent supportive care information available.

#### **Section 11.2 and Appendix 4**

- Modified text to state that selinexor tablets (20 mg) will be supplied in polyvinyl chloride/polychlorotrifluoroethylene/polyvinyl chloride (PVC/PCTFE/PVC) film blisters (or equivalent) with an aluminum foil lidding in a secondary paper wallet with childproofing to reflect current information.

#### **Section 11.4.6**

- Removed text to align with the selinexor *Investigator's Brochure: Alcohol*: Ethanol should be avoided on selinexor dosing days as it may compete for GSH-mediated metabolism

#### **Section 12.1.1**

- Revised text to align with Table 9.

#### **Section 15:**

- Added references to the list that were inadvertently removed from previous versions of the protocol.
- Added Durie 2006, [Kumar 2016](#), and [Rajkumar 2011](#) to the list of references
- Removed Kyle 2009 and Palumbo 2014 from the list of references

#### **Appendix 7:**

Some of the detailed information in the Protocol Version 4 ROW SOC was not included in the Protocol Version 4 SOC for the US because the Protocol Version 4 ROW SOC was revised after Protocol Version 4 for the US was published.

## Amendment 4

### Protocol Version 5.0

#### Amendment Rationale

The primary purpose for this amendment was to address comments received from Regulatory Authorities.

The revised protocol Version 5.0 dated 28 April 2017 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A summary of key changes that were made to protocol Version 4.1, including rationales for these changes, is provided below.

#### Changes to the Protocol

##### *Administrative Changes*

- Updated the version number and date of protocol (**Modified sections:** Global)
- Updated the number of patients who have received selinexor to the number based on the most recent Investigator's Brochure (31 March 2017) (Modified sections: Global)
- Internal changes to improve clarity (Modified sections: Global)

##### *Specific Content Changes*

#### Protocol Approval Signature Page

- Replaced Humphrey Gardner, M.D., Senior Vice President, Clinical Development, with Michael Kauffman, MD, PhD, Acting Chief Medical Officer, as a signatory.

#### Synopsis

- Added the following text to the Background and Study Rationale to align with the most recent IB, “across all patients was 21% and the clinical benefit rate (CBR) is 33%. Similar ORR were seen in the patients with “penta” and “quad” MM, with higher CBR in patients who received 8 vs. 6 doses/cycle consistent with improved disease control with continuous dosing.”
- Added the following text, “If any patient is not able to tolerate this dose, then a potential discontinuation or further decrease in dosage would be allowed after a discussion with the Medical Monitor on a case by case basis,” to allow for adjustments to the dosing of dexamethasone.

#### Inclusion/Exclusion Criteria (also in Synopsis and Sections 8.4 and 8.5)

- Modified inclusion criteria #10 to clarify that female patients of childbearing potential must agree to use 2 methods of contraception (including 1 highly effective and 1 effective method of contraception).
- Modified inclusion criteria #13 to remove “on Cycle 1 Day 1” for hemoglobin level  $\geq$  8.5 g/dL.

- Modified inclusion criteria #14 to add “key” to specific criteria.
- Corrected exclusion criteria #17 to add  $\geq$  to Grade 2 painful neuropathy

**Table 1 (Schedule of Assessments)** (also in Section 9.7.2.4)

- Modified footnote #8 to, “For females of childbearing potential; negative serum hCG pregnancy test must be obtained within 3 days before the first dose of study treatment. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of Cycles  $\geq 2$  and at the EoT Visit (serum hCG). Pregnancy testing may also be performed as clinically indicated during the study,” to required that testing is performed on Day 1 of Cycles  $\geq 2$ .
- Modified footnote #12 to clarify that bone marrow aspirates for MRD analysis are to be collected at response for CR or sCR, not at sCR only.
- Removed blood draws for PDn and PK analysis and footnotes #14 and #15 as PK and PDn blood samples are no longer being collected; updated previous footnotes #16 to #14, #17 to #15, and #18 to #16.

**List of Abbreviations:**

- Removed definition for FLC (kappa/lamba ratio) for clarification
- Added definition for TRAE (treatment-emergent adverse event)

**Protocol, Main Body**

**Section 4.3**

- Updated the clinical experience sections to the most recent safety and efficacy information for MM in the KCP-330-001 study and for KCP-330-012 study in the IB.

**Section 4.4**

- Updated the information on ACS to reflect the current selinexor safety information.

**Section 5.1**

- Added the following text, “If any patient is not able to tolerate this dose, then a potential discontinuation or further decrease in dosage would be allowed after a discussion with the Medical Monitor on a case by case basis,” to allow for adjustments to the dosing of dexamethasone.

**Section 9.2**

- Updated text to reflect IMWG requirement for sequential sample to confirm response, “SPEP with serum protein immunofixation, quantitative Ig, serum FLC, and 24-hour UPEP, with immunofixation, must be collected at each required time point. An aliquot of the blood and urine samples should be retained. If the local laboratory results indicate a CR or sCR, a sequential sample, per IMWG, should be collected and analyzed. Aliquots from the initial and subsequent collection will be sent to the central laboratory to confirm the CR or sCR response.”
- Corrected in Table 4 that karyotyping and FISH will be performed at a central laboratory, not a local laboratory.

#### **Table 4**

- Modified text that bone marrow aspirates will be collected for MRD analysis on patients who achieve CR or sCR, not sCR only.

#### **Section 9.3**

- Updated text to specify that all MM assessments are required at each time point. Added text to clarify the timing of collection of sequential MM assessment samples, “Two consecutive samples are required to confirm the response. The time period between samples may be discussed with the Medical Monitor and can occur on the same day, as long as, the samples are analyzed separately.”

#### **Section 9.4.4**

- Added new Section, Pregnancy Testing, with the following text: “For females of childbearing potential, a negative serum human chorionic gonadotropin (hCG) pregnancy test must be obtained within 3 days before the first dose of study treatment. Test sensitivity for hCG must be  $\geq 25$  mIU/mL. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of Cycles  $\geq 2$  during the study and at the EoT Visit (serum hCG). Pregnancy testing may also be performed as clinically indicated during the study.”

#### **Sections 9.5.1, 9.7.2.1, 9.7.2.2 and Table 6**

- Replaced text in these sections with, “As of protocol version 5.0, these samples are no longer collected.” Table 6 was removed as the PK and PDn blood samples are no longer being collected as it is not necessary to continue collecting these samples.

#### **Section 9.7.2.3**

- Changed volume of Screening bone marrow aspirate from 1x6 mL to 2x10mL to provide sufficient material for PDn tests. Specified that karyotyping and FISH will be performed at a central laboratory.

#### **Section 9.2.7.4**

- Modified text that MRD analysis may be performed on samples of bone marrow aspirates collected at the time of response in patients who achieve CR or sCR, not sCR only.

#### **Section 11.1.3**

- Added the following text, “If any patient is not able to tolerate this dose, then a potential discontinuation or further decrease in dosage would be allowed after a discussion with the Medical Monitor on a case by case basis,” to allow for adjustments to the dosing of dexamethasone.
- Added text to clarify that PK and PDn sampling only occurs in protocol versions  $< 5.0$ .

#### **Section 11.1.5.5**

- Added text to clarify that PK and PDn sampling only occurs in protocol versions  $< 5.0$ .

#### **Section 11.2 and Appendix 4**



- Modified text to simplify the description of the blister packaging.

#### **Section 11.4.7**

- Revised Prevention of Pregnancy language to Contraception Requirements to clarify that female patients of childbearing potential must agree to use 2 methods of contraception (including 1 highly effective and 1 effective method of contraception).

#### **Section 12.1.3.1**

- Added the Karyopharm German PV fax number for European sites.
- Revise text to modify reporting suspected unexpected serious adverse reactions to the competent authorities and relevant ethics committees in accordance with the FDA's "Safety Reporting Requirements for Investigational New Drugs and Bioanalytical/Bioequivalence Studies" or as per national regulatory requirements in participating countries in order to ensure safety information is reported to authorities in all countries participating in the study.

#### **Section 14.11**

- Clarified the publication language to include the following text, "Publication will be in a relevant peer- reviewed journal, with authorship status and ranking designated according to the acknowledged contributions of participating investigators, institutions and the Sponsor."

#### **Section 15**

- Added Vogl 2016 to the list of references

#### **Appendix 7:**

- Revised Changes to the Protocol for Protocol Version 4.1 to accurately capture changes made to that version of the protocol.



## Amendment 5

### Protocol Version 6.0

#### Amendment Rationale

The primary purpose for this amendment was to update statistical language (e.g., definition of analysis populations, exploratory endpoints) and to address inconsistencies.

The revised protocol Version 6.0 dated 13 December 2017 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A summary of key changes that were made to protocol Version 5.0, including rationales for these changes, is provided below.

#### Changes to the Protocol

##### *Administrative Changes*

- Updated the version number and date of protocol (**Modified sections:** Global)
- Internal changes to improve clarity (Modified sections: Global)

##### *Specific Content Changes*

#### Protocol Approval Signature Page

- Replaced Michael Kauffman, M.D, PhD, Acting Chief Medical Officer, with Jatin Shah Kauffman, MD, Vice President, Clinical Strategy, as a signatory.

#### Synopsis

- Objectives: updated for consistency with the Statistical Analysis Plan:
  - Updated definitions of Durations of CBR and DCR.
  - Updated exploratory endpoints.
- Statistical Methods: updated the definition of mITT and PP populations, for consistency with SAP, and removed the presentation of exploratory EE population (details to be provided SAP only).

#### Table 1 (Schedule of Assessments) (also in Section 9.2)

- Modified footnotes #2 and #9 to indicate that results of pre-screening MM assessments at Day -30 (window: Screening – 2 weeks) and Day -60 ( $\pm 15$  days) will be provided. This information is required to more fully understand history of patient's MM (extent of disease, rate of progression).

#### Protocol, Main Body

##### Section 4.1

- Updated the Introduction for clarity and accuracy.

##### Section 6.2

- Updated definitions of Durations of CBR and DCR, for consistency with the SAP.

### **Section 7.3**

- Deleted the following text, as IRC does not review disease assessments at the time of progression and discontinuation of treatment does not require confirmation of PD by IRC: "...and must review at time of progression. Progression based on site generated disease assessment data must be confirmed by the IRC prior to discontinuing treatment."

### **Section 8.2**

- Removed Canada from the list of countries where the study is being conducted, to reflect that the study is not being conducted in Canada.

### **Section 8.8**

- Added the following text after date of birth, "(as allowed by regulatory authorities)" to clarify that investigator should provide birth date information in compliance with their regulatory authorities.

### **Section 9.1.2, 9.2**

- Added text to indicate that results of pre-screening MM assessments at Day -30 (window: Screening – 2 weeks) and Day -60 ( $\pm 15$  days) will be provided. This information is required to more fully understand history of patient's MM (extent of disease, rate of progression).
- Text edited in Section 9.2 to clarify sample collection and analysis procedures in the event of a CR or sCR, to align with the lab manual.

### **Table 4**

- Removed the following text: "If sufficient bone marrow aspirate material is not available at the required time points, a bone marrow core (trephine) biopsy should be performed." The follow-up core biopsy should no longer be performed.

### **Section 9.7.2.3**

- Added text to provide additional details on use and storage of bone biopsy aspirate samples to be used for pharmacogenomic research.

### **Section 13.2.1**

- For consistency with Statistical Analysis Plan:
  - Updated the definition of mITT and PP populations
  - Removed presentation of exploratory EE population (details to be provided SAP only)
  - Updated Sub-group Efficacy Analyses

### **Section 13.3.4**

- Updated the definition of mITT and PP populations, and removed the exploratory EE population definition, for consistency with Statistical Analysis Plan.

**Appendix 7:**

- Added Summary of Changes for Protocol Version 6.0 to describe changes made to version 5.0.

**STATISTICAL ANALYSIS PLAN****Protocol KCP-330-012**

**A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) Plus Low-Dose Dexamethasone (Sd) in Patients with Multiple Myeloma Previously Treated with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib, and Daratumumab, and Refractory to Prior Treatment with Glucocorticoids, an Immunomodulatory Agent, a Proteasome Inhibitor, and the anti-CD38 mAb Daratumumab**

<b>Protocol Version:</b>	<b>5.0</b>
<b>Type of Analysis Plan:</b>	<b>Final Analysis</b>
<b>Version:</b>	<b>1.0</b>
<b>Date:</b>	<b>12 December 2017</b>
<b>Author:</b>	<b>Lingling Li, PhD</b>

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**STATISTICAL ANALYSIS PLAN SIGNATURE PAGE**

The undersigned has developed this statistical analysis plan (SAP):

<b>Name/Title</b>	<b>Signature</b>	<b>Date</b>
Lingling Li, PhD Associate Director, Biostatistics		

The undersigned have reviewed this SAP and approve it in its entirety:

<b>Name/Title</b>	<b>Signature</b>	<b>Date</b>
Shijie Tang, PhD Senior Director, Biostatistics		

**DOCUMENT HISTORY**

<b>Version</b>	<b>Date</b>	<b>Author(s)</b>	<b>Brief Summary of Changes</b>
1.0	December 12, 2017	Lingling Li	Original

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**LIST OF ABBREVIATIONS AND DEFINITION OF TERMS**

<b>Abbreviation</b>	<b>Definition</b>	<b>Abbreviation</b>	<b>Definition</b>
AE	adverse event	mITT	modified intent-to-treat
ALT	alanine transaminase (SGPT)	MM	multiple myeloma
aPTT	activated partial thromboplastin time	MR	minimal response
AST	aspartate transaminase (SGOT)	MRD	minimal residual disease
ATC	Anatomic Therapeutic Class	NCI	National Cancer Institute
Bpm	beats per minute	OR	odds ratio
BSA	body surface area	ORR	overall response rate
BUN	blood urea nitrogen	OS	overall survival
C1D1	Cycle 1 Day 1	PD	progressive disease
CBR	clinical benefit rate	PDn	pharmacodynamic
CI	confidence interval	PFS	progression free survival
CR	complete response	PI	proteasome inhibitor
CSR	clinical study report	PK	pharmacokinetic
CTCAE	Common Terminology Criteria for Adverse Events	PP	per protocol
DCR	disease control rate	PR	partial response
DOR	duration of response	PT	preferred term
ECG	electrocardiogram	QoL	quality of life
ECOG	Eastern Cooperative Oncology Group	QRS	the portion of an electrocardiogram comprising the Q, R, and S waves, together representing ventricular depolarization
eCRF	electronic case report form	QTcB	QT interval corrected by Bazett's formula
EDTA	ethylenediaminetetraacetic acid	QTcF	QT interval corrected by Fridericia's formula
EFS	event-free survival	SAE	serious adverse event
EoS	eosinophil count - absolute	SAP	statistical analysis plan
EoT	End of Treatment	SAS	Statistical Analysis System
ETDRS	Early Treatment Diabetic Retinopathy Study	sCR	stringent complete response
FACT-G	Functional Assessment of Cancer Therapy – General	SD	stable disease
FACT-MM	Functional Assessment of Cancer Therapy – Multiple Myeloma	Sd	selinexor 80 mg plus dexamethasone 20 mg ("low-dose" dexamethasone)
FISH	fluorescent in situ hybridization	SI	International System of Units
FLC	free light chain	SOC	system organ class
GGT	gamma-glutamyl transferase	SPEP	serum protein electrophoresis
HCO3	bicarbonate	TEAE	treatment-emergent adverse event
Hgb	hemoglobin	TOI	trial outcomes index
IMiD	immunomodulatory drug	TSH	thyroid stimulating hormone
IMWG	International Myeloma Working Group	TTP	time to progression
INR	international normalization ratio	ULN	upper limit of normal
IRC	Independent Review Committee	UPEP	urine protein electrophoresis
ISS	International Staging System	VGPR	very good partial response
ITT	intent-to-treat	WBC	white blood cell
LDH	lactate dehydrogenase	WHO	World Health Organization
LLN	lower limits of normal	WHO DDE	World Health Organization Drug Dictionary Enhanced
MedDRA	Medical Dictionary for Regulatory Activities	XPO1	exportin 1
mg	Milligram		

## 1. OVERVIEW AND INVESTIGATIONAL PLAN

### 1.1. STUDY DESIGN

KCP-330-012 is a Phase 2b, single-arm, open-label, multicenter study of Sd (selinexor 80 mg plus dexamethasone 20 mg), both dosed twice weekly, for each week of a four-week cycle, in patients with multiple myeloma (MM) previously treated with alkylating agents, glucocorticoids, lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and the anti-CD38 mAb daratumumab (i.e., penta-refractory MM). Note: refractory is defined as  $\leq 25\%$  response to therapy, progression during the previously described therapies, or progression within 60 days after completion of the therapy (per International Myeloma Working Group [IMWG] criteria 2016).

This study consists of two parts and will enroll approximately 210 patients overall. Part 1 (protocol V1.0-3.0) enrolled patients with both quad-refractory MM (i.e., previously treated with alkylating agents, glucocorticoids, lenalidomide, pomalidomide, bortezomib, carfilzomib, but not an anti-CD38 mAb, and refractory to prior treatment with glucocorticoids, an IMiD, and a PI) along with patients that had quad-refractory MM and whose disease was refractory to an anti-CD38 monoclonal antibody. Part 2 (protocol V $\geq$ 4.0) will enroll patients with penta-refractory MM only where the anti-CD38 monoclonal antibody is daratumumab.

The population for the primary efficacy analysis will contain only patients with penta-refractory MM enrolled in Part 2. Efficacy results for patients with quad-refractory MM and patients with penta-refractory MM enrolled in Part 1 will be analyzed separately. Safety analyses will be performed on the Part 2 patients with penta-refractory MM, the overall safety population of patients who received any amount of study treatment, presented overall and by study part.

Patients receive selinexor 80 mg plus dexamethasone 20 mg (Sd), both dosed twice weekly, for each week of four-week cycles. Patients will receive treatment until progressive disease (PD), death, toxicity that cannot be managed by standard care, or withdrawal, whichever occurs first.

Patients will also receive best supportive care to mitigate selinexor side effects, including blood product transfusions, antimicrobials, and (as appropriate) growth factors including granulocyte colony-stimulating factors for neutropenia, erythropoietins for anemia, and/or platelet-stimulating factors for thrombocytopenia.

In select cases (e.g., for patients showing stable disease [SD] or partial response [PR] and tolerating treatment particularly well), the selinexor dose may be increased by 20 mg after consultation with the Medical Monitor. The dose level for an individual patient may be escalated based on efficacy considerations only after a minimum of 2 cycles of study therapy. However, in no case may the dose for any patient exceed 70 mg/m<sup>2</sup>. Prior to any potential dose increase, the BSA for the patient will be calculated and an individual patient's dose may not be increased if it would result in a dose > 70 mg/m<sup>2</sup>.

In Part 2, MM-specific assessments (i.e., serum protein electrophoresis [SPEP], urine protein electrophoresis [UPEP], serum/urine immunofixation, quantitative Ig levels, serum free light chain [FLC], and bone marrow aspirate) must be confirmed by a central laboratory to confirm complete response (CR) or stringent complete response (sCR), per IMWG consensus criteria. Additional information is provided in the *Study Manual*.

Patients may decide to discontinue study treatment for any reason. Patients who elect to discontinue study treatment should be encouraged to continue in the study so that follow-up information on disease progression, other antineoplastic therapy, symptoms and survival status may be obtained. However, patients may elect to withdraw consent and decline further participation in the trial at any time. The Investigator may remove a patient from study treatment using criteria described in Section 10.2 of Protocol V5.0.

The Investigator must determine the primary reason for a patient's discontinuation of study treatment and record this information on the electronic case report form (eCRF). Patients who are prematurely withdrawn from study treatment are not eligible to re-initiate study treatment on this protocol at a later date.

## **1.2. OBJECTIVES**

### **1.2.1. Primary Objectives**

Evaluate the efficacy (overall response rate [ORR]) for treatment with selinexor 80 mg plus low-dose dexamethasone (20 mg) (Sd) twice weekly (four-week cycles) in patients with penta-refractory MM previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab; and refractory to prior treatment with glucocorticoids, an IMiD, a PI, and the anti-CD38 mAb daratumumab.

ORR will include patients who experience PR, very good partial response (VGPR), CR, or sCR, based on IMWG response criteria (*Kumar 2016*). The ORR for patients with penta-refractory MM in Part 2 will be compared to a minimal threshold level of 10%.

### **1.2.2. Secondary Objectives**

The following endpoints will be analyzed separately for (a) Part 1 patients with quad-refractory MM, (b) Part 1 patients with penta-refractory MM, and (c) Part 2 patients with penta-refractory MM. Additionally, analyses of safety and tolerability will be performed on the overall population of patients from Parts 1 and 2 who received at least one dose of study treatment.

- Duration of response (DOR = Duration from first observation of at least PR to time of PD, or death due to disease progression, whichever occurs first. DOR will be censored for death due to any causes other than disease progression.
- Clinical Benefit Rate (CBR = sCR + CR + VGPR + PR + minimal response [MR]), and duration of clinical benefit (Duration from first observation of at least MR to time of PD, or death due to disease progression, whichever occurs first. Duration of clinical benefit will be censored for death due to any cause other than disease progression.
- Disease Control Rate (DCR = CBR + SD [for a minimum of 12 weeks])
- Progression Free Survival (PFS = Duration from start of study treatment to PD or death [regardless of cause], whichever comes first)
- Time to Progression (TTP = Duration from start of study treatment to time of PD) obtained with selinexor plus dexamethasone vs. TTP on most recent prior therapy
- Time to Next Treatment (TTNT = Duration from start of study treatment to start of next anti-MM treatment or death due to disease progression, whichever occurs first)

- Overall Survival (OS = Duration from start of study treatment to death)
- Quality of Life (QoL) using the Functional Assessment of Cancer Therapy - Multiple Myeloma (FACT-MM)
- Safety and tolerability using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v 4.03.
- Describe the Pharmacokinetics (PK) properties of selinexor in this patient population (Part 1 only)

### 1.2.3. Exploratory Objectives

The following endpoints will be analyzed for Part 2 patients with penta-refractory MM:

- ORR and TTNT for the patient's last treatment regimen vs. for the study treatment
- ORR, DOR, PFS, and OS in patients with Revised International Staging System (R-ISS) stage I, II, and III respectively. R-ISS stage is defined as follows:
  - A patient is classified as R-ISS stage I if the patient had baseline serum  $\beta_2$ -microglobulin level  $< 3.5$  mg/L and baseline serum albumin level  $\geq 3.5$  g/dL, had no high-risk chromosomal abnormalities (del (17p)/p53, t(14; 16), or t(4; 14)), and had normal lactate dehydrogenase (LDH) at baseline. Refer to Section 2.5 for the definition of baseline measurement. Chromosomal abnormality determination can be based on any assessment prior to the first dose of study drug.
  - A patient is classified as R-ISS stage III if the patient had serum  $\beta_2$ -microglobulin level  $> 5.5$  mg/L at baseline, and either have high-risk chromosomal abnormalities [del (17p)/p53, t(14; 16), or t(4; 14)] or had high LDH level (above upper limit normal) at baseline.
  - A patient is classified as R-ISS II if the patient was not classified as R-ISS stage I or III.
- Minimal residual disease (MRD) in patients who achieve CR, and sCR, and selected patients who achieve VGPR.
- Correlational studies to evaluate response to treatment with selinexor as related to:
  - Cytogenetic and fluorescent *in situ* hybridization (FISH) prognostic markers, including p53 abnormalities and chromosomal aberrations (e.g., del 17p, t(4;14), t(14;16), del 13) and other MM cytogenetic classifications
  - R-ISS stage (I vs. II vs. III)
  - Time since initial diagnosis of active myeloma
  - Lytic lesions as assessed by skeletal survey (or similar bone imaging)

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data in order to answer the study objectives. Populations for analysis, data handling rules, and statistical methods are provided. This SAP does not include endpoints and methods to be used in the analysis of PK data; these will be included in a separate plan.

### 1.3. DETERMINATION OF SAMPLE SIZE

The sample size for this study addresses the primary study objective of evaluating the clinical effect of Sd in patients with penta-refractory MM by reference to a minimal threshold level for ORR, set to 0.10 (10%). Note that the original sample size estimation for the study in Part 1 was based on clinical assumptions for patients with quad-refractory MM, and the assumptions have been updated for patients with penta-refractory MM.

Based on preliminary evidence from Part 1 of this study, it is believed that selinexor plus dexamethasone may exhibit substantial efficacy; therefore, the statistical test associated with the comparison to the threshold will maintain a Type I error rate of 0.025, 1-sided.

For the primary efficacy analysis, a sample size of 122 patients with penta-refractory MM will allow a 1-sided test at  $\alpha=0.025$  to detect an ORR of  $\geq 0.20$  against the threshold ORR of 0.10, with 90% power.

Overall, a total of ~210 patients will be enrolled, including 122 enrolled patients with penta-refractory MM (Part 2; Versions  $\geq 4.0$ ) for the primary analysis and 79 previously enrolled patients in Part 1 (78 patients with measurable disease at baseline, 30 patients with penta-refractory MM and 48 patients with quad-refractory MM enrolled under Versions  $<4.0$ ) for additional secondary and exploratory analyses.

### 1.4. STUDY PLAN

For each patient that signs the informed consent, the study consists of:

- Screening/baseline visit: occurs within 21 days prior to receiving the 1<sup>st</sup> dose of study treatment
- Treatment period: expected to be up to 12 months, but there is no maximum treatment duration. Patients will be treated until disease progression, death, toxicity that cannot be managed by standard care, or withdrawal from study, whichever occurs first
- Follow-up period: up to 12 months after last dose of study treatment, patients will be contacted approximately every 3 months for durability of response and survival follow-up

The End of Study (EoS) will occur when all patients have completed the 12-month follow-up period (i.e., when the last patient has expired, been followed for 12 months after last dose of study treatment, been lost to follow-up, or has withdrawn consent, whichever occurs first).

Please refer to Table 7-1 for detailed schedule of assessment and study activities.

### 1.5. INTERIM ANALYSIS

No interim analysis is planned for this study.

### 1.6. DATABASE LOCK

The primary analysis will be performed after all patients have completed the Cycle 3 MM Assessments, and will include a formal database lock and analyses of efficacy, safety, and PK data. A clinical study report (CSR) will be prepared after the primary analysis.



At the time of the database lock for the primary analysis, the median DOR estimate may not be estimable with limited follow-up time. Therefore, an efficacy update on ORR and DOR among the Part 2 patients with penta-refractory MM will be provided before the submission of the New Drug Application (NDA) package.

The final analysis will be performed at the end of the study after all patients have completed the 12-month follow-up period (i.e., when the last patient has expired, been followed for 12 months after last dose of study treatment, been lost to follow-up, or has withdrawn consent, whichever occurs first). There will be a formal database lock and analyses of efficacy and safety data. A final CSR will be prepared summarizing the results from the full analysis.

## **1.7. MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL**

The current SAP is based on Protocol v5.0. The following modifications were made to the statistical section of protocol.

### **Analysis Populations**

- Additional analysis populations for efficacy endpoints and additional safety populations (Sections 3.1.1, 3.1.2, and 3.1.3) are defined to present data in a comprehensive manner.
- The definition of the modified intent-to-treatment (mITT) population is revised to include patients who did not meet all eligibility criteria but received Sponsor waiver to participate in the study. Waivers are not granted to patients who do not meet key eligibility criteria such as required prior therapies and measurable disease at baseline.
- The definition of the per-protocol population is revised (Section 3.1.1). The requirement of having completed at least one cycle of treatment is removed. Instead, patients are required to have at least one adequate post-baseline response assessment unless they died or withdrew from the study before that. Moreover, patients are required to have a compliance rate of at least 70% of selinexor instead of 80%.

### **Secondary Efficacy Endpoints**

- The censoring rules for the secondary endpoints of duration of clinical benefits is revised to follow the TTP rule, such that it is consistent with the censoring rule for duration of response.
- The endpoint of duration of disease control is removed.
- The secondary endpoint of TTNT is added.

### **Subgroup Analysis**

- Subgroup analysis by R-ISS stage (I vs. II vs. III), region (US vs. non-US), and FLC MM patient (yes vs. no) respectively are added to explore potential effect modification by these factors.

### **Exploratory Objective**

- The R-ISS stage is used instead of the original ISS stage as the former also considers high risk chromosomal abnormalities and LDH level.

- DOR for the patient's last treatment regimen is replaced with TTNT.

## **1.8. STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN**

Not applicable

## **2. GENERAL STATISTICAL METHODS AND DATA HANDLING**

### **2.1. GENERAL ANALYSIS METHODS**

This is a single-arm, open-label study. All summary statistics will be computed and displayed among the corresponding analysis population, and by each scheduled assessment time point whenever applicable. Summary statistics for continuous variables will minimally include n, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries. Graphical displays will be provided as appropriate.

### **2.2. MISSING DATA HANDLING IN DATA PRESENTATION**

In general, missing baselines will not be imputed. The following approaches are default methods for missing data handling in summary tables.

- Categorical data at baseline will be summarized using counts (n) and percentages (%). Denominator will be the analysis population specified for the summary, unless otherwise specified. Missing data may be presented as a separate category.
- Continuous data: summaries will be based on observed data only.

#### **2.2.1. Handling of Computation of Treatment Duration if Study Treatment End of Treatment Date is Missing**

For the calculation of treatment duration, the date of the last dose of study treatment is equal to the date of last study treatment dosing reported on study treatment dosing form. If all the dosing dates are missing, then the duration is missing.

The last dose intake should be clearly identified on the eCRF dosing page and should not be approximated by the last returned package date.

#### **2.2.2. Handling of Missing/partial Dates for Adverse Events or Concomitant Medications**

In general, the imputation should be conservative such that onset dates should be imputed to be as early as possible and resolution dates will be imputed to be as late as possible. Impute resolution date first and then impute onset date using imputed resolution date. However, for categorization purpose, if the partial AE onset date information does not indicate whether the AE started prior to treatment or after the treatment-emergent adverse event (TEAE) period, the AE will be classified as treatment-emergent.

These data imputations are for categorization purpose or calculation of AE duration, and will not be used in listings. In data listings, an ongoing flag will be identified from the eCRF AE page.

Refer to the Karyopharm Biostatistics and Statistical Programming Rule Book for details on imputation methods.

#### **2.2.3. Handling of Missing or Partial Birth Date for Calculation of Age**

Refer to the Karyopharm Biostatistics and Statistical Programming Rule Book for details on imputation methods.

#### **2.2.4. Handling of AEs When Date and Time of First Dose of Study Treatment Are Missing**

When the date and time of the first dose of study treatment are missing, all AEs that occurred on or after signing the informed consent should be considered as TEAEs. The exposure duration should be kept as missing.

#### **2.2.5. Handling of Missing Assessment of Relationship of AEs to Study Treatment**

If the assessment of the relationship to study treatment is missing, then the relationship to study treatment in the frequency tables is considered as possibly related, but no imputation should be done at the data level or in data listings.

#### **2.2.6. Handling of Missing Severity of AEs**

If the severity is missing for one of the treatment-emergent occurrences of an AE, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a “missing” category will be added in the summary table.

### **2.3. STUDY TREATMENT DOSING DATE**

Study treatment dosing date is the date on which a patient actually received study treatment (selinexor plus dexamethasone, partial or complete).

The date of first study treatment is defined as the earliest date of non-zero dose of either selinexor or dexamethasone. The date of last study treatment is defined as the latest date of non-zero dose of either selinexor or dexamethasone.

### **2.4. STUDY DAY CALCULATION**

Based on the study protocol, study Day 1 is the first study treatment dosing date. The day before Day 1 is considered Day -1; there is no Day 0.

A patient is considered as treated in a cycle if the patient received any non-zero dose of either selinexor or dexamethasone in that cycle.

Study day for a given assessment is defined as

- the assessment date – the date of first study treatment + 1 if the assessment date is on or after Day 1, or
- the assessment date – the date of first study treatment if the assessment date is before Day 1.

### **2.5. BASELINE MEASUREMENT**

In general, the baseline value is defined as latest value prior to the first dose of study treatment. In the case an assessment performed on the same date as the first dose, but it is impossible to determine the evaluation time relative to the time of taking the first dose, the evaluation time will be assumed to be following the protocol-defined schedule.

For the variables related to MM assessment, clinical laboratory variables, and several other safety variables, when data are available, values from Cycle 1 Day 1 (C1D1, prior to the first dose of study treatment) will be used as baseline values; otherwise, the Screening value or the value from the latest unscheduled visit before C1D1 will substitute as the baseline value.

## 2.6. VISIT WINDOWS

For the safety analyses (laboratory and vital signs), if needed, the nominal visit as stated in the protocol will be used for the by-visit type of summaries. Unscheduled visit measurements of laboratory data and vital signs will not be included in the by-visit summaries, but will be used for computation of baseline, worst and last values, and status, and will be included in data listings.

## 2.7. SUBGROUPS

Subgroup analysis on selected efficacy endpoints will be conducted by

- R-ISS for MM (stage I, II, and III respectively)
- Region (US vs. non-US).
- FLC MM patient (yes vs. no), a FLC MM patient is defined as a patient without measurable disease in SPEP or UPEP, but with measurable disease in FLC, all based on baseline value.

## 2.8. POOLING OF CENTERS FOR STATISTICAL ANALYSES

All participating centers in the study will be pooled together for analysis.

## 2.9. COMPUTING AND CODING STANDARDS

Activities will be performed using the following tools:

<b>Table, listing, and figure production</b>	SAS Version 9.4 or higher
<b>Coding</b>	
AEs	MedDRA Version 20.1
Medical Histories	MedDRA Version 20.1
Prior and Concomitant Medications	WHO DDE Version March 2017
<b>Grading</b>	
AEs	CTCAE Version 4.0
Labs	CTCAE Version 4.03

### 3. PATIENT INFORMATION

#### 3.1. DISPOSITION OF PATIENTS AND ANALYSIS POPULATIONS

This study consists of two parts. Part 1 (Protocol v1.0-3.0) enrolled patients with both quad-refractory MM and penta-refractory MM. Part 2 (Protocol v $\geq$ 4.0) enroll patients with penta-refractory MM only.

Patient disposition will be summarized for Part 1 and Part 2 patients separately. Patient study status will be summarized in each of the following categories:

- Screened patients, defined as any patient who has signed the informed consent form
- Screen failure patients and reasons for screen failure
- Patients who met study eligibility criteria (including patients who did not meet all eligibility criteria per the protocol in effect at the time of enrollment but received waiver from Sponsor) but did not receive any dose of study treatment (partial or complete)
- Patients who met study eligibility criteria (including patients who did not meet all eligibility criteria per the protocol in effect at the time of enrollment but received waiver from Sponsor) and received at least one dose of study treatment (partial or complete)
- An end-of-treatment disposition:
  - Patients who were still on treatment
  - Patients who discontinued treatment and primary reason for treatment discontinuation
- An end-of-study disposition:
  - Patients who were still on study
  - Patients who withdrew from study and primary reason for study withdrawal

##### 3.1.1. Efficacy Populations

The efficacy populations will only include patients from Part 2. Results for Part 1 patients will be summarized and analyzed separately.

The ***modified intent-to-treat (mITT) population*** will consist of Part 2 patients with penta-refractory MM who met all eligibility criteria (or did not meet all eligibility criteria but received waiver from Sponsor to participate in the study), and received at least one dose of study treatment (partial or complete). This population will include patients who have discontinued therapy due to toxicity or PD and patients who have died from any cause, including those related to study treatment or disease. The mITT population will be used for the primary efficacy analyses.

The ***per-protocol (PP) population*** will consist of all patients in the mITT population who meet the following criteria:

- Have selinexor compliance  $\geq 70\%$ , see Section 3.4.2 for the definition of selinexor compliance rate.

- Have at least one adequate post-baseline response assessment unless died or withdrew from study before that.
- No major protocol violations that would compromise the assessment of efficacy. The list of major protocol violations that affect statistical analysis will be finalized before database lock.

The ***BCLPD-ref population*** will consist of patients in Part 2 who had documented refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab, and received at least one dose of study treatment (partial or complete).

The ***CLPD-ref population*** will consist of patients in Part 2 who had documented refractory to carfilzomib, lenalidomide, pomalidomide, and daratumumab, and received at least one dose of study treatment (partial or complete).

The ***BCPD-ref population*** will consist of patients in Part 2 who had documented refractory to bortezomib, carfilzomib, pomalidomide, and daratumumab, and received at least one dose of study treatment (partial or complete).

The ***CPD-ref population*** will consist of patients in Part 2 who had documented refractory to carfilzomib, pomalidomide, and daratumumab, and received at least one dose of study treatment (partial or complete).

The PP, BCLPD-ref, CLPD-ref, BCPD-ref, CPD-ref populations will be used for supportive inferences concerning efficacy.

A patient is claimed to have documented refractory to a therapy if one of the following criteria is met:

- Best response on the therapy is SD or worse
- Patient progressed or relapsed during treatment
- Patient progressed or relapsed within 60 days after discontinuing this therapy.

If the date of treatment discontinuation or the date of disease progression/relapse is missing (partially or completely), unless it can be determined that one of the above criteria is met (e.g., both dates have day missing, but have the same year and month), the patient is determined to not have documented refractory.

### **3.1.2. Safety Population**

The safety population will consist of all patients from Part 1 and Part 2, who have received at least one dose of study treatment (partial or complete) and have any post-baseline safety information.

Safety outputs will be presented by the following groups:

- Overall safety population
- The subset of safety population from Part 2, i.e., the mITT population
- The subset of safety population from Part 1

### 3.1.3. Additional Analysis Populations

Analysis of selected efficacy endpoints will be conducted in the following populations respectively:

The **high-risk population** will consist of all Part 2 patients with penta-refractory MM with any of the following high-risk chromosomal abnormalities including del (17p)/p53, t(14; 16), t(4; 14), and 1q21, and received at least one dose of study treatment (partial or complete). Chromosomal abnormality determination can be based on any assessment before the first dose of study drug.

The **Part 1 quad-ref MM population** (Part 1 – Quad) will consist of all quad-refractory patients in Part 1 who received at least one dose of study treatment (partial or complete).

The **Part 1 penta-ref MM population** (Part 1 – Penta) will consist of all penta-refractory patients in Part 1 who received at least one dose of study treatment (partial or complete).

The **Part 1 six doses per cycle population** (Part 1 – 6 doses) will consist of all patients in Part 1 who were dosed with Sd twice weekly for 3 weeks out of 4-week cycle.

The **Part 1 eight doses per cycle population** (Part 1 – 8 doses) will consist of all patients in Part 1 who were dosed with Sd twice weekly for 4 weeks out of 4-week cycle.

Selected safety endpoints will be summarized within the Part 1 - Quad, Part 1 - Penta, Part 1 – 6 doses, and Part 1 – 8 doses populations respectively.

## 3.2. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

In general, the baseline value is defined as latest value prior to the first dose of study treatment.

### 3.2.1. Demographic Data

Demographic variables include sex (female, male), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other), ethnicity, and age at study entry.

### 3.2.2. Prior Therapies

Prior therapies for MM will be summarized with the following variables:

- Exposure/refractory status to each individual MM treatment including lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, alkylating agent, glucocorticoid, anthracyclines, and stem cell transplant
- Refractory status to at least one IMiD, one PI, and daratumumab
- Refractory status to all five therapies including bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab
- Refractory status to all five therapies except bortezomib
- Refractory status to all five therapies except lenalidomide
- Refractory status to carfilzomib, pomalidomide, and daratumumab
- Number of prior systemic therapies (summarized as a continuous variable and as a categorical variable) and months from most recent prior systemic therapy to start of study treatment

The duration to be summarized is defined as follows.



- Months from most recent prior systemic therapy to start of study treatment will be calculated as (date of first dose of study treatment – stop date of most recent systemic therapy +1)/ (365.25/12).

The detailed history of prior cancer therapies including best response, whether patient progressed or relapsed during or after treatment will be presented in a data listing.

### **3.2.3. Medical/surgical History**

Medical/surgical history will be summarized in the mITT population by system organ class (SOC) and preferred term (PT) using the number and percentage of patients who had at least one occurrence of a SOC and PT. The summary will be sorted by alphabetic order in SOC, and further by decreasing frequency of PT within each SOC in the mITT population. When more than one PT has the same frequency, the order of presentation will be alphabetical in PTs.

### **3.2.4. Disease History**

Disease history includes disease stage at initial diagnosis, disease stage at active myeloma, current disease stage according to ISS (or R-ISS if parameters available) for MM, and the following results at initial diagnosis:  $\beta_2$  microglobulin, albumin, immunoglobulin type, light chain type, availability of bone marrow results, % plasma cells, and availability of FISH results. Smoking history including status (Never used, Current, Former), and frequency when applicable will also be recorded.

### **3.2.5. Physical Examination and Vital Signs**

At screening, a full physical examination will be performed including height (without shoes) in centimeters (cm), weight (indoor clothing without shoes) in kilograms (kg), temperature, heart rate, systolic and diastolic blood pressure, and oxygen saturation. Significant findings that were present prior to the signing of informed consent must be included on the eCRF medical history page. Significant new findings, including the presence of plasmacytomas, that begin or worsen after informed consent must be recorded on the eCRF AE or Plasmacytoma page.

### **3.2.6. Eastern Cooperative Oncology Group (ECOG) Score**

The ECOG performance status (Grade 0-5) will be recorded at screening.

### **3.2.7. Analysis Methods**

Continuous data will be summarized using the number of available observations, mean, standard deviation, median, minimum, and maximum. Categorical and ordinal data will be summarized using the number and percentage of patients with the denominators for the percentages determined based on the analysis population used, unless otherwise specified. Demographics and baseline characteristics will be summarized among mITT, PP, BCLPD-ref, CLPD-ref, BCPD-ref, and CPD-ref populations respectively. P-values on demographic and baseline characteristic data will not be calculated. No specific description of the safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety analysis.

### **3.3. CONCOMITANT MEDICATIONS AND PROCEDURES**

#### **3.3.1. Concomitant Medications and Procedures**

Concomitant medication consists of any prescription or over-the-counter preparation, including vitamins, dietary supplements, over-the-counter medications, and oral herbal preparations. Patients may continue their baseline medication(s). Concomitant medications include all medications used to mitigate AEs such as nausea, for supportive care, to treat or prevent infection, or to maintain the use of dexamethasone in combination of selinexor in this study. All concomitant medication(s) must be reported on the eCRF. Any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s), and any clinical findings, if applicable.

All medications will be coded using the WHO DDE Version March 2017.

- Prior medications are any treatments received by the patient prior to the first dose of study treatment. Prior medications can be discontinued before first dose of study treatment or can be ongoing during treatment period
- Concomitant medications are any treatments received by the patient concomitantly with study treatment, from first dose of study treatment to last dose of study treatment + 30 days
- Post-treatment medications are those the patient took in the period running from the 30 days after last dose of study treatment up to the end of the study

#### **3.3.2. Analysis Methods**

Concomitant medications will be summarized according to the WHO DDE dictionary using the mITT population, by the anatomic and therapeutic class (ATC) level 2 (therapeutic level) and level 4 (generic level). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category linked to the medication. Therefore, patients may be counted several times for the same medication. The summary will be sorted by decreasing frequency in ATC level 2 and then ATC level 4 in the mITT population.

Prior medications and procedures will be presented in data listing only. Note that a medication can be classified as both a prior medication and a concomitant medication.

Please refer to Section 2 for details on data handling rules related to computation, dates, imputation for missing dates.

### **3.4. EXTENT OF STUDY TREATMENT EXPOSURE AND COMPLIANCE**

The extent of study treatment exposure and compliance will be summarized in safety population.

#### **3.4.1. Extent of Study Treatment Exposure**

The extent of exposure for the study treatment will be assessed using the following variables:

- Duration of study treatment exposure
- Number of cycles treated (continuous and categorical)

- Number of selinexor doses received
- Number of dexamethasone dose received
- Number and percentage of patients with a selinexor dose reduction
- Number and percentage of patients with a dexamethasone dose reduction
- Number and percentage of patients with a selinexor dose interruption
- Number and percentage of patients with a dexamethasone dose interruption
- Number and percentage of patients with study treatment discontinued

Duration of study treatment exposure is defined as the date of last study treatment - date of first study treatment + 1, regardless of unplanned intermittent discontinuation.

### 3.4.2. Compliance

Study treatment compliance will be summarized descriptively as a quantitative variable among the mITT population, calculated as

$$\frac{\text{number of study treatment doses taken}}{\text{number of study treatment doses prescribed}} \times 100.$$

A study treatment dose is considered prescribed if selinexor and/or dexamethasone is prescribed. The number and percentage of patients with study treatment compliance  $\geq 70\%$  will be provided. Note that the number of prescribed study treatment doses does not include doses missed due to treatment interruption or other reasons not related to patient choice.

Selinexor compliance is defined similarly among the mITT population as

$$\frac{\text{number of selinexor doses taken}}{\text{number of selinexor doses prescribed}} \times 100.$$

The number and percentage of patients with selinexor compliance  $\geq 70\%$  will be provided. Similarly, the number of prescribed selinexor doses does not include doses missed due to treatment interruption or other reasons not related to patient choice. Patients with selinexor compliance  $< 70\%$  will be excluded from the PP population.

## 4. EFFICACY

Patient response at each time point will be assessed centrally by an IRC according to the IMWG response criteria (*Kumar 2016*) for MM. Unless otherwise specified, MM response assessment refers to assessment determined by IRC.

Documentation of response requires two consecutive readings of the applicable disease parameter (serum M-protein, urine M-protein, serum FLC, or quantitative immunoglobulin level), performed at any time with no minimum interval required between the two readings. The date of response or PD will be assigned to the earlier date of the two independent samples, unless PD is based on an unambiguous criterion such as a new plasmacytoma lesion.

If a patient had one progressive disease assessment but was not subsequently confirmed, unless IRC considers the progression assessment unambiguous, it is not considered a PD (*Kumar 2016*).

Unless otherwise specified, efficacy analyses will use the mITT population. Analyses for the primary efficacy endpoint of ORR and the key secondary efficacy endpoints of DOR, CBR, and duration of clinical benefit will be repeated in the other efficacy populations and additional analysis populations. Other selected efficacy analyses will be repeated in the other efficacy populations if relevant.

### 4.1. PRIMARY EFFICACY ENDPOINT

#### 4.1.1. Definition

The primary endpoint is ORR which is defined as the proportion of patients who achieve a confirmed PR or better (i.e., PR, VGPR, CR, or sCR) during or after the study treatment, before documented disease progression or initiating a new MM treatment.

#### 4.1.2. Primary Analysis of ORR

For the primary analysis of superiority to the minimal threshold ORR, analysis will be performed using the 2-sided, exact 95% confidence interval (CI), calculated for the rate of ORR among the mITT population, and statistical significance will be declared if the lower bound of this interval is greater than 10%.

#### 4.1.3. Supportive Analyses of ORR

For exploratory purposes, ORR rates and CIs will also be calculated:

- Using the PP, BCLPD-ref, CLPD-ref, BCPD-ref, CPD-ref, high-risk, Part 1 – Quad, Part 1 – Penta, Part 1 – 6 doses, and Part 1 – 8 doses populations respectively
- Based on Investigator assessment
- With ORR defined as the proportion of patients who achieve an unconfirmed PR or better
- From patient's last treatment regime, when data are available
- In patients with R-ISS for MM stage I, II, and III respectively
- In US vs. non-US patients

- In FLC MM vs. non-FLC MM patients

No formal hypothesis testing will be conducted to compare the ORR rates in the subgroup analysis.

## **4.2. SECONDARY EFFICACY ENDPOINTS**

Several of the secondary efficacy endpoints define durations based on either the progression free survival (PFS) status and time, or time to progression (TTP) status and time. In PFS, death with any cause is considered as an event. In TTP, only death due to disease progression is considered as an event. Please refer to Table 4-1 and Table 4-2 for details on censoring rules for PFS and TTP respectively.

### **4.2.1. Duration of Response (DOR)**

#### **4.2.1.1. Definition**

DOR is defined for patients with a confirmed PR or better as the duration from first observation of at least PR to time of IRC-determined PD or death due to disease progression, whichever occurs first. The censoring method for DOR is the same as the censoring method for TTP in Table 4-2.

#### **4.2.1.2. Analysis Methods**

DOR will be summarized descriptively among those with a confirmed PR or better. Median DOR with 95% CI will be estimated based on the Kaplan-Meier method. The Kaplan-Meier curve for the duration of response will be provided.

#### **4.2.1.3. Supportive Analyses of DOR**

As supportive analyses, median DOR and 95% CI will be calculated:

- Using the PP, BCLPD-ref, CLPD-ref, BCPD-ref, CPD-ref, high-risk, Part 1 – Quad, Part 1 – Penta, Part 1 – 6 doses, and Part 1 – 8 doses populations respectively, if sufficient data exist
- In patients with R-ISS for MM stage I, II, and III respectively, if sufficient data exist
- In US vs. non-US patients, if sufficient data exist
- In FLC MM vs. non-FLC MM patients, if sufficient data exist.

### **4.2.2. Clinical Benefit Rate (CBR)**

#### **4.2.2.1. Definition**

CBR is defined as the proportion of patients who achieve a confirmed MR or better, i.e., MR, PR, VGPR, CR, sCR. Duration of clinical benefit is defined as the duration from first observation of at least MR to time of IRC-determined PD or death due to disease progression, whichever occurs first. Responders without IRC-determined PD or death due to disease progression will be censored at the censored date for TTP.

#### **4.2.2.2. Analysis Methods**

The rate of CBR and the 2-sided, exact 95% CI will be calculated using the mITT population. Median duration of clinical benefit with 95% CI will be estimated based on the Kaplan-Meier method. The Kaplan-Meier curve for the duration of clinical benefit will be provided.

The number and percentage of patients in the individual response categories (MR, PR, VGPR, CR, sCR) based on best response will be calculated respectively.

As supportive analyses, CBR rate and 95% CI will be calculated:

- Using the PP, BCLPD-ref, CLPD-ref, BCPD-ref, CPD-ref, high-risk, Part 1 – Quad, Part 1 – Penta, Part 1 – 6 doses, and Part 1 – 8 doses populations respectively.
- In patients with R-ISS for MM stage I, II, and III respectively
- In US vs. non-US patients
- In FLC MM vs. non-FLC MM patients.

Median duration of clinical benefit with 95% CI will be calculated in these analysis populations and subgroups when sufficient data exist.

#### **4.2.3. Disease Control Rate (DCR)**

##### **4.2.3.1. Definition**

DCR is defined as the proportion of patients who achieve SD for a minimum of 12 weeks, or better (i.e., SD for a minimum of 12 weeks, MR, PR, VGPR, CR, sCR).

##### **4.2.3.2. Analysis Methods**

The rate of DCR and the 2-sided, exact 95% CI will be calculated using the mITT population.

As supportive analyses, DCR rate and 95% CI will be calculated:

- Using the PP, BCLPD-ref, CLPD-ref, BCPD-ref, and CPD-ref populations respectively, if sufficient data exist

#### **4.2.4. Progression Free Survival (PFS)**

##### **4.2.4.1. Definition**

PFS is defined as the duration from start of study treatment to time of IRC-determined PD or death from any cause, whichever occurs first. Please refer to Table 4-1 for details on PFS outcome status (PFS event vs. censored) and date definition. Unless otherwise specified, PD status refers to confirmed PD or PD by unambiguous criteria based on IRC assessment. If PD is based on 2 independent samples on an applicable disease parameter, date of PD refers to the earlier date of the 2 independent samples.

##### **4.2.4.2. Analysis Methods**

A duration is calculated as end date – start date + 1. For instance, if a PFS event occurs, then PFS time (in days) is defined as event date – start date of study treatment + 1. If a censoring event occurs, then PFS time is defined as the censoring date – start date of study treatment + 1.

**Table 4-1 PFS outcome and censoring definition**

<b>Situation</b>	<b>Date of event or censoring</b>	<b>Outcome</b>
No adequate post-baseline disease status assessment unless death occurs prior to first post-baseline assessment	Start of study treatment	Censored
Death before IRC-determined PD without a gap of 2 or more consecutively missed scheduled disease status assessment before death	Death date	PFS event
IRC-determined PD without a gap of 2 or more consecutively missed scheduled disease status assessment before progression	Date of PD	PFS event
No IRC-determined PD or death on or before <ul style="list-style-type: none"> <li>• database cut,</li> <li>• withdrawal of informed consent,</li> <li>• lost to follow-up,</li> <li>• documented treatment discontinuation</li> <li>• start of new MM treatment, whichever occurs first</li> </ul>	Date of last adequate disease assessment prior to the earliest occurrence of the events listed in the left column	Censored
No IRC-determined PD or death before a gap of 2 or more consecutively missed scheduled disease status assessment	Date of last adequate disease assessment prior to the gap	Censored

Median PFS with 95% CI will be estimated based on the Kaplan-Meier method. The Kaplan-Meier curve for PFS will be provided.

The following supportive analyses will be conducted:

- PFS based on Investigator assessment
- PFS in the PP, BCLPD-ref, CLPD-ref, BCPD-ref, and CPD-ref populations respectively, if sufficient data exist

#### **4.2.5. Time to Progression (TTP)**

##### **4.2.5.1. Definition**

TTP is defined as the duration from start of study treatment to time of IRC-determined PD or death due to disease progression, whichever occurs first. Please refer to Table 4-2 for details on

TTP outcome status and date definition. Unless otherwise specified, PD assessment refers to assessment determined by IRC. But for the cause of death, disease progression refers to investigator assessment as specified on the eCRF death report page.

#### 4.2.5.2. Analysis Methods

**Table 4-2 TTP outcome and censoring definition**

Situation	Date of event or censoring	Outcome
No adequate post-baseline disease status assessment unless death due to disease progression occurs prior to first post-baseline assessment	Start of study treatment	Censored
Death due to disease progression before IRC-determined PD without a gap of 2 or more consecutively missed scheduled disease status assessment before death	Death date	TTP event
IRC-determined PD without a gap of 2 or more consecutively missed scheduled disease status assessment before progression	Date of disease progression	TTP event
No IRC-determined PD or death due to disease progression on or before <ul style="list-style-type: none"> <li>• Death due to reasons other than disease progression</li> <li>• database cut,</li> <li>• withdrawal of informed consent,</li> <li>• lost to follow-up,</li> <li>• documented treatment discontinuation</li> <li>• start of new MM treatment, whichever occurs first</li> </ul>	Date of last adequate disease assessment prior to the earliest occurrence of the events listed in the left column	Censored
No IRC-determined PD or death due to disease progression before a gap of 2 or more consecutively missed scheduled disease status assessment	Date of last adequate disease assessment prior to the gap	Censored

Median TTP with 95% CI will be estimated based on the Kaplan-Meier method. The Kaplan-Meier curve for TTP will be provided.



The following supportive analyses will be conducted:

- TTP based on Investigator assessment
- TTP in the PP, BCLPD-ref, CLPD-ref, BCPD-ref, and CPD-ref populations respectively, if sufficient data exist
- TTP on most recent prior therapy

#### **4.2.6. Time to Next Treatment (TTNT)**

##### **4.2.6.1. Definition**

TTNT is defined as the duration from start of study treatment to start of next anti-MM treatment or death due to disease progression, whichever occurs first. The censoring method for TTNT is the same as the censoring method for TTP.

##### **4.2.6.2. Analysis Methods**

Median TTNT with 95% CI will be estimated based on the Kaplan-Meier method. The Kaplan-Meier curve for TTNT will be provided.

The following supportive analyses will be conducted:

- TTNT in the PP, BCLPD-ref, CLPD-ref, BCPD-ref, and CPD-ref populations respectively, if sufficient data exist
- TTNT on most recent prior therapy

#### **4.2.7. Overall Survival (OS)**

##### **4.2.7.1. Definition**

OS is defined as the duration from start of study treatment to death from any cause. If death event did not occur during the follow-up period, the patient is censored at the date of discontinuation from the study, or database cut date, whichever is earlier.

##### **4.2.7.2. Analysis Methods**

The proportion of patients with death event and the 2-sided, exact 95% CI will be calculated using the mITT population. Median OS time with 95% CI will be estimated based on the Kaplan-Meier method. The Kaplan-Meier curve for OS will be provided.

The following supportive OS analyses will be conducted:

- Using the PP, BCLPD-ref, CLPD-ref, BCPD-ref, CPD-ref populations respectively
- Using the high-risk, Part 1 – Quad, Part 1 – Penta, Part 1 – 6 doses, and Part 1 – 8 doses respectively, if sufficient data exist
- The same as in primary OS analysis except additional censoring at the start date of a new MM treatment
- In patients with R-ISS for MM stage I, II, and III respectively, if sufficient data exist
- In US vs. non-US patients, if sufficient data exist
- In FLC MM vs. non-FLC MM patients, if sufficient data exist

- In patients with a best response of confirmed PR or better
- In patients with a best response of confirmed MR or better
- In patients with a best response of MR
- In patients with a best response of SD or worse (including not evaluable patients)

#### **4.2.8. Quality of life (QoL)**

##### **4.2.8.1. Definition**

Health-related QoL and potential for improvement over the course of the study will be assessed using the Functional Assessment of Cancer Therapy – Multiple Myeloma (FACT-MM) patient-reported outcome questionnaire that is specifically relevant to MM. This instrument combines the general version of the FACT (FACT-G) with a MM-specific subscale (14 items). The subscales for the FACT-G are Physical Well-Being (7 items), Social/Family Well-Being (7 items), Emotional Well-Being (6 items), and Functional Well-Being (7 items). The trial outcomes index (TOI; total of 41 items) will be the primary measurement of interest, comprised of the Physical and Functional subscales plus the MM-specific subscale. Each item is rated on a 5-point Likert scale, ranging from 0 (“Not at all”) to 4 (“Very much”), therefore the TOI has a score ranging from 0 to 120. The QoL assessment will be performed at Baseline (prior to first dose of study treatment), Day 1 of each cycle on or after the second, and at the Final visit.

##### **4.2.8.2. Analysis Methods**

The primary analysis for QoL will be based on the change from baseline on the TOI score at each assessment time point, which will be summarized using descriptive statistics including mean, standard deviation, median, minimum, and maximum. The total score considering all 5 subscales as well as the 5 individual subscale sums of scores will be summarized similarly.

The following supportive analyses will be conducted:

- In patients with a best response of confirmed PR or better
- In patients with a best response of confirmed MR or better

### **4.3. EXPLORATORY EFFICACY ANALYSES**

#### **4.3.1. Minimal Residual Disease (MRD)**

MRD will be assessed at response for CR or sCR patients, and selected VGPR patients, by analyzing bone marrow aspiration specimens. A status of positive vs. negative will be assigned.

The numbers and percentages of patients with MRD positive vs. negative status respectively at the time of response will be presented among those patients with a confirmed CR or sCR, as well as selected patients with a confirmed VGPR.

#### **4.3.2. Correlative Studies**

Contingent upon availability of sufficient data, multivariable logistic regression models will be fit to the mITT population to evaluate response to study treatment as related to the following factors (all evaluated at baseline):

- FISH prognostic markers including p53 abnormalities and chromosomal aberrations (e.g., del 17p, t(4;14), t(14;16), del 13) and other MM cytogenetic classifications will be explored.
- Time since initial diagnosis of active myeloma
- Lytic lesions as measured by skeletal survey (or similar bone imaging,  $\leq 2$  vs. 3+)
- R-ISS stage (I vs. II vs. III)

Two response definitions will be explored:

- whether the patient achieved a confirmed response of PR or better
- whether the patient achieved a confirmed response of MR or better.

The independent variables for the logistic regression will also include age and region (US vs. non-US).

Corresponding odds ratios (ORs) with 2-sided 95% CIs, as well as the p-values indicating statistical significance will be presented.

## 5. SAFETY

Safety analyses will use the safety population with the outputs presented by the following groups:

- Overall safety population
- The subset of safety population from Part 2, i.e., the mITT population
- The subset of safety population from Part 1

Safety analyses will be based on the reported AEs and other safety information, such as 12-lead electrocardiogram (ECG), ophthalmic exam, clinical laboratory assessments including hematology, serum chemistry, coagulation parameters, and urinalysis, vital signs, physical examination, and pregnancy testing.

### *Observation period*

The observation period will be divided into the following periods:

- The pre-treatment period is defined as the time from the signed informed consent date up to first dose of study treatment.
- The treatment period is defined as the time from first dose of study treatment to last dose of study treatment + 30 days inclusive.
- The post-treatment period is defined as the time beyond the treatment period.

The on-study observation period is pre-treatment, treatment, and post-treatment period.

### *General rules*

All safety analyses will be performed using the following common rules:

- Safety data in patients who do not belong to the safety population (e.g., enrolled but did not receive any dose of study treatment, partial or complete) will be listed separately.
- The baseline value is the last available value before the first dose of study treatment.
- The analyses of the safety variables will be essentially descriptive and no systematic testing is planned.

## 5.1. ADVERSE EVENTS

### 5.1.1. Definitions

An AE is defined as any undesired medical occurrence in a patient or clinical investigation patient receiving a pharmaceutical product regardless of a causal relationship with this treatment. An AE can therefore be any unfavorable sign and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a study treatment, whether or not related to the study treatment.

***AE observation period***

- Pre-treatment AEs are AEs that developed or worsened or became serious from the signed informed consent up to first dose of study treatment.
- ***Treatment-emergent adverse events (TEAE)*** are defined as any AE that developed or worsened or became serious during the treatment period; or any AE with a start date after the first dose of study treatment, and is considered related to study treatment by the Investigator. Note that any AE that was present at baseline but worsened in toxicity grade after first dose of study treatment, and is subsequently considered as related to study treatment shall be considered as TEAE.
- Post-treatment AEs are AEs that developed or worsened or became serious during post-treatment period and is not considered TEAE.

All AEs (including serious adverse events [SAEs]) will be coded to a PT and associated primary SOC using the MedDRA version 20.1.

The severity of all AEs will be graded according to the CTCAE Grading Scale. An AE with a CTCAE grade of 3 or higher is considered a severe AE. The severity of the AE is different from the seriousness of the AE which is defined below. For AEs not covered by CTCAE, the severity will be characterized as “mild,” “moderate,” or “severe” according to the following definitions:

- Mild events are usually transient and do not interfere with the patient’s daily activities.
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Severe events interrupt the patient’s usual daily activities.

***Serious adverse events***

A SAE is any untoward medical occurrence that occurs at any dose (including after the informed consent form is signed and prior to dosing) that:

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

SAE needs to be clearly documented on the patient’s AE form.

**5.1.2. Analysis Methods**

The primary focus of AE reporting will be on TEAEs. Pre- and post-treatment AEs will be described separately.

If an AE date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pre-treatment, treatment-emergent, or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment-emergent unless there is definitive information to determine it is

pre-treatment or post-treatment. Details on classification of AEs with missing or partial onset dates are provided in Section 2.2.2.

AE summaries will include number (n) and percentage (%) of patients experiencing an AE. The denominator for computation of percentages is the number of patients in the corresponding population.

Unless otherwise specified, sorting order will follow the alphabetic order in SOC, and further by decreasing number of events in PTs within each SOC. When more than one PT has same number of events, the order of presentation will be alphabetical in PTs.

Multiple occurrences of the same event in the same patient will be counted only once in the tables.

Based on the entries on the eCRF AE page,

- An AE is considered potentially related to study treatment if:
  - the entry for “Relationship to selinexor” is either “Possibly Related” or “Related”, or
  - the entry for “Relationship to Dexamethasone” is either “Possibly Related” or “Related”.
- An AE is considered potentially related to selinexor if the entry for “Relationship to selinexor” is either “Possibly Related” or “Related”.
- An AE is considered potentially related to dexamethasone if the entry for “Relationship to Dexamethasone” is either “Possibly Related” or “Related”.

#### **5.1.2.1. Analysis of TEAEs**

An overview table summarizing the following will be presented:

- TEAEs
- Severe TEAEs (CTCAE Grade  $\geq 3$ )
- Serious TEAEs
- TEAEs potentially related to either selinexor or dexamethasone
- TEAEs potentially related to selinexor only
- TEAEs potentially related to dexamethasone only
- TEAEs not related to selinexor or dexamethasone
- Serious TEAEs potentially related to either selinexor or dexamethasone
- Serious TEAEs potentially related to selinexor only
- Serious TEAEs potentially related to dexamethasone only
- Serious TEAEs not related to selinexor or dexamethasone
- TEAEs leading to death
- TEAEs leading to permanent treatment discontinuation

TEAEs will be summarized by primary SOC and PT and will include the following categories:

- All TEAEs
- All TEAEs, by relatedness
  - TEAEs potentially related to either selinexor or dexamethasone
  - TEAEs potentially related to selinexor only
  - TEAEs potentially related to dexamethasone only
  - TEAEs not related to selinexor or dexamethasone
- All TEAEs, by maximum grade
- Grade 3 or higher TEAEs
- Grade 3 or higher TEAEs, by relatedness
  - Grade 3 or higher TEAEs potentially related to either selinexor or dexamethasone
  - Grade 3 or higher TEAEs potentially related to selinexor only
  - Grade 3 or higher TEAEs potentially related to dexamethasone only
  - Grade 3 or higher TEAEs not related to selinexor or dexamethasone
- TEAEs leading to selinexor dose reduced or drug interrupted
- TEAEs leading to dexamethasone dose reduced or drug interrupted
- Grade 3 or higher TEAEs leading to selinexor dose reduced or drug interrupted
- TEAEs leading to withdrawn from selinexor treatment
- Grade 3 or higher TEAEs leading to withdrawn from selinexor treatment

The most commonly reported (at least 10% of all patients) TEAEs will be presented by PT only and will include the following categories:

- The most commonly reported TEAEs
- The most commonly reported TEAEs potentially related to study treatment

#### **5.1.2.2. Analysis of SAEs**

Treat-emergent SAEs will be summarized by primary SOC and PT and will include the following categories:

- All treatment-emergent SAEs
- Treatment-emergent SAEs, by relatedness
  - Treatment-emergent SAEs potentially related to either selinexor or dexamethasone
  - Treatment-emergent SAEs potentially related to selinexor only
  - Treatment-emergent SAEs potentially related to dexamethasone only

- Treatment-emergent SAEs not related to selinexor or dexamethasone
- Treatment-emergent SAEs leading to selinexor dose reduced or drug interrupted
- Treatment-emergent SAEs leading to dexamethasone dose reduced or drug interrupted
- Treatment-emergent SAEs leading to withdrawal from selinexor treatment

Data listings will be provided for the following AE categories:

- All TEAEs
- All treatment-emergent SAEs
- All Grade 3 or higher TEAEs
- All TEAEs leading to withdrawal from selinexor treatment
- All pre- and post-treatment AEs

## **5.2. DEATH**

The following summaries on death events will be provided:

- An overview of all death events and primary cause of death
- TEAEs leading to death (death as an outcome on the AE report page as reported by the Investigator), by primary SOC and PT
- TEAEs leading to death and are potentially related to study treatment, by primary SOC and PT
- Listing of all death events

## **5.3. LABORATORY SAFETY VARIABLES**

### **5.3.1. Definitions**

Clinical laboratory data consists of blood analysis, including hematology, serum chemistry, coagulation parameters, and urinalysis. Clinical laboratory values in conventional units will be converted using the international system of units (SI).

Blood samples for clinical laboratory tests will be taken as specified in the study protocol. The laboratory parameters will be classified as follows:

- Hematology (blood sample: ethylenediaminetetraacetic acid [EDTA]) tests including hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count, WBC differential, red blood cell count, lymphocytes, monocytes, neutrophils, eosinophils, basophils, and platelets. WBC differential may be automated or manual as per institutional standards.
- Serum Chemistry (blood sample: serum)
  - Complete Serum Chemistry will include sodium, potassium, chloride, bicarbonate ( $\text{HCO}_3^-$ ), blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphate, magnesium, alanine aminotransferase (ALT), aspartate aminotransferase (AST),



alkaline phosphatase, total bilirubin and lactate dehydrogenase (LDH), total protein, albumin, amylase, lipase, creatine kinase and uric acid.

- Limited Serum Chemistry will include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin and LDH, unless otherwise clinically indicated.
- Thyroid-stimulating hormone (TSH)
- Coagulation parameters will include prothrombin time, international normalization ratio (INR), and activated partial thromboplastin time (aPTT).
- Urinalysis will include appearance, color, urine bilirubin, glucose, hemoglobin, ketones, pH, protein, specific gravity, and urobilinogen. Microscopy will only be performed if clinically indicated.

### 5.3.2. Analysis of Laboratory Variables

Whenever applicable, severity of selected clinical laboratory measures will be determined based on the CTCAE criteria. Laboratory values with CTCAE Grade  $\geq 3$  will be presented in a data listing. The worst toxicity grade in hematology and chemistry will be summarized by toxicity grade. Shift tables that present changes from baseline to worst on-study and baseline to last on-study values relative to CTCAE classification ranges will be presented.

For several key laboratory parameters (i.e., sodium, creatinine, platelet, hemoglobin, WBC, BUN-to-creatinine ratio, urea-to-creatinine ratio), box plots on measurements over time as well as by-patient plots for patient-level measurements over time will be presented.

A listing of possible Hy's law cases (ALT or AST  $> 3 \times$  upper limit of normal [ULN] with simultaneous total bilirubin  $> 2 \times$  ULN) will be presented. The elevations of ALT/AST and total bilirubin must occur within 2 days of each other.

Thresholds/Range analyses for selected laboratory, vital signs, and ECG parameters will be conducted. Please refer to Appendix 7.2 for the definitions on thresholds/ranges for selected parameters. The number and percentage of patients classified into each category based on worst values will be presented.

## 5.4. VITAL SIGNS, ECOG, AND PHYSICAL EXAMINATION VARIABLES

Full physical examinations with vital signs are performed only during screening and end-of-treatment (EoT) visits, including height (without shoes) in centimeters (cm) [measured during screening visit only], weight (indoor clothing without shoes) in kilograms (kg), temperature, heart rate, systolic and diastolic blood pressure, and oxygen saturation.

At other visits, symptom-directed physical examinations are conducted with vital signs (temperature, heart rate, systolic and diastolic blood pressure).

An ECOG score assessment with grades 0-5 will be performed during screening, day 1 of each cycle, and the EoT visit.

Shift tables that present changes from baseline to worst on-study and last on-study for systolic blood pressure, diastolic blood pressure, and ECOG performance status values will be produced.

Abnormal vital signs results will be summarized in the threshold/range analyses as defined in Appendix 7.2.

All vital signs, ECOG, and physical examination findings will be presented in data listings.

### **5.5. ELECTROCARDIOGRAM (ECG)**

Standard 12-lead ECGs will be performed during screening and EoT visits. Patients must rest for at least 5 minutes prior to the ECG recording. The Investigator will interpret the ECG using one of the following categories: normal, abnormal but not clinically significant, or abnormal and clinically significant. The following will be assessed: heart rate, rhythm, interval from start of the Q wave to the end of the S wave (QRS), interval from the beginning of the P wave until the beginning of the QRS complex (PR Interval), interval between the start of the Q wave and the end of the T wave (QT), and QT corrected (QTc) using Bazett's formula or calculated by the Fridericia correction formula (*Bazett 1920, Fridericia 1920*). If Bazett correction is entered by the site, the Fridericia corrected QTc interval (QTcF) will be derived using the formula:  $QT/(RR^{1/3})$ , where  $RR = 60/\text{heart rate}$ .

Abnormal ECG results will be summarized in the threshold/range analyses as defined in Appendix 7.2.

Electrocardiogram data for each patient will be provided in a data listing.

### **5.6. OPHTHALMIC EXAM**

A full ophthalmic examination will be performed during the Screening and EoT visits. Prior to dilation, best corrected visual acuity (Snellen's Equivalent based on either Snellen chart or Early Treatment Diabetic Retinopathy Study [ETDRS chart]), and slit lamp examination including tonometry will be conducted. Following dilation, funduscopy will be conducted. Please refer to Protocol v5.0 for details on the grading of cataract if seen during the examination.

All ophthalmic examination findings will be presented in a data listing.

## 6. REFERENCES

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3. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med*. 1987;317:1098.

## 7. APPENDICE

### 7.1. Appendix I: Schedule of Assessments

**Table 7-1 Schedule of Assessments and Study Activities**

Activity/Assessment	Screening	Cycle 1				Cycle 2		Cycles $\geq 3$	End-of-Treatment (EoT) Visit	Safety Follow-up Call	Durability of Response and Survival Follow-up <sup>15</sup>
	Day -21 to Day -1	Day 1	Day 3 <sup>14</sup>	Day 8	Day 15	Day 1	Day 15	Day 1	$\leq 14$ Days Post Last Dose	30 Days Post-Last Dose	Every 3 mo.
		-1 day	+1 day	$\pm 1$ day	$\pm 1$ day	$\pm 2$ days	$\pm 2$ days	$\pm 2$ days		+ 7 days	$\pm 14$ days
Informed consent <sup>1</sup>	X										
Inclusion/exclusion criteria	X										
Demographics	X										
Medical history <sup>2</sup>	X	X									
Patient height	X										
Patient weight	X	X		X	X	X	X	X	X		
Body Surface Area (BSA) <sup>3</sup>	X										
Physical examination, full including vital signs <sup>4</sup>	X								X		

Activity/Assessment	Screening	Cycle 1				Cycle 2		Cycles $\geq 3$	End-of-Treatment (EoT) Visit	Safety Follow-up Call	Durability of Response and Survival Follow-up <sup>15</sup>
	Day -21 to Day -1	Day 1	Day 3 <sup>14</sup>	Day 8	Day 15	Day 1	Day 15	Day 1	$\leq 14$ Days Post Last Dose	30 Days Post-Last Dose	Every 3 mo.
		-1 day	+1 day	$\pm 1$ day	$\pm 1$ day	$\pm 2$ days	$\pm 2$ days	$\pm 2$ days		+ 7 days	$\pm 14$ days
Physical examination, symptom-directed, including vital signs <sup>4</sup>		X		X	X	X	X	X			
ECOG <sup>5</sup>	X					X		X	X		
Echocardiogram or MUGA <sup>6</sup>	X										
12-lead ECG	X								X		
Ophthalmic exam <sup>7</sup>	X								X		
Clinical Labs											
Urinalysis <sup>5</sup>	X								X		
CBC with differential <sup>5</sup>	X				X	X	X	X	X		
TSH <sup>5</sup>	X								X		
Complete serum chemistry <sup>5</sup>	X					X		X	X		

Activity/Assessment	Screening	Cycle 1				Cycle 2		Cycles $\geq 3$	End-of-Treatment (EoT) Visit	Safety Follow-up Call	Durability of Response and Survival Follow-up <sup>15</sup>
	Day -21 to Day -1	Day 1	Day 3 <sup>14</sup>	Day 8	Day 15	Day 1	Day 15	Day 1	$\leq 14$ Days Post Last Dose	30 Days Post-Last Dose	Every 3 mo.
		-1 day	+1 day	$\pm 1$ day	$\pm 1$ day	$\pm 2$ days	$\pm 2$ days	$\pm 2$ days		+ 7 days	$\pm 14$ days
Limited serum chemistry				X	X		X				
Coagulation tests <sup>5</sup>	X								X		
Serum hCG pregnancy test <sup>8</sup>	X					X (D1 of each cycle only)		X (D1 of each cycle only)	X		
C-reactive protein	X	X				X		X	X		
Multiple Myeloma Assessments											
SPEP and serum protein immunofixation <sup>9</sup>	X	X				X		X	X		X
UPEP (24-hr urine for total protein) and urine protein immunofixation <sup>9</sup>	X	X				X		X	X		X
Quantitative Ig levels <sup>9</sup>	X	X				X		X	X		X

Activity/Assessment	Screening	Cycle 1				Cycle 2		Cycles $\geq 3$	End-of-Treatment (EoT) Visit	Safety Follow-up Call	Durability of Response and Survival Follow-up <sup>15</sup>
	Day -21 to Day -1	Day 1	Day 3 <sup>14</sup>	Day 8	Day 15	Day 1	Day 15	Day 1	$\leq 14$ Days Post Last Dose	30 Days Post-Last Dose	Every 3 mo.
		-1 day	+1 day	$\pm 1$ day	$\pm 1$ day	$\pm 2$ days	$\pm 2$ days	$\pm 2$ days		+ 7 days	$\pm 14$ days
Serum FLC <sup>9</sup>	X	X			X	X	X	X	X		X
$\beta_2$ -microglobulin	X								X		
Skeletal survey <sup>10</sup>	X					(X)		(X)	X		(X)
Plasmacytoma assessment <sup>11</sup>	X					(X)		(X)	X		(X)
Bone marrow aspirate <sup>12</sup>	X					(X)		(X)			(X)
Bone marrow core biopsy <sup>13</sup>	X					(X)					
FACT-MM questionnaire	X					X		X	X		
Study treatment dosing		Selinexor 80 mg + dexamethasone 20 mg (both twice weekly) for 4 weeks (each week) of 4-week cycles									
Adverse events <sup>16</sup>	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X		

Activity/Assessment	Screening	Cycle 1				Cycle 2		Cycles $\geq 3$	End-of-Treatment (EoT) Visit	Safety Follow-up Call	Durability of Response and Survival Follow-up <sup>15</sup>
	Day -21 to Day -1	Day 1	Day 3 <sup>14</sup>	Day 8	Day 15	Day 1	Day 15	Day 1	$\leq 14$ Days Post Last Dose	30 Days Post-Last Dose	Every 3 mo.
		-1 day	+1 day	$\pm 1$ day	$\pm 1$ day	$\pm 2$ days	$\pm 2$ days	$\pm 2$ days		+ 7 days	$\pm 14$ days
Nutritional consultation	X										
Telephone contact <sup>14</sup>			X							X	X
Antineoplastic therapy after EoT									X	X	X

(X) indicates that additional information is provided in the footnotes. Merged cells indicate that the procedure may be performed during either Screening or the CID1 visit.

Abbreviations: BSA = body surface area; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoT = End of Treatment; Ig = immunoglobulin; MM = multiple myeloma; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; CBC = complete blood count; FLC = free light chain.

<sup>1</sup> Prior to the first study-specific measure.

<sup>2</sup> Including details of all prior anti-myeloma therapies. Includes baseline symptoms as well as a detailed history of prior cancer therapies, especially MM therapies, including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness.

<sup>3</sup> Body Surface Area (BSA) will be calculated by *Dubois 1916* or *Mosteller 1987* method during Screening and prior to any dose escalation. No patient may receive a dose of selinexor  $> 70$  mg/m<sup>2</sup>.

<sup>4</sup> Complete physical examination (PE) during Screening and EoT visit. Limited PEs during the study should be symptom directed. All PEs to include vital signs (blood pressure, pulse and body temperature).

<sup>5</sup> The following procedures may be performed at Screening or pre-dose on CID1 and as shown in the Schedule during the study: ECOG performance assessment, echocardiogram or MUGA scan, 12-lead ECG, ophthalmic exam, urinalysis, CBC with differential, TSH, complete serum chemistry, coagulations tests, and nutritional consultation.

<sup>6</sup> Echocardiogram or MUGA scan at Screening and as clinically indicated during the study.

<sup>7</sup> A full ophthalmic examination will include, prior to dilation, best corrected visual acuity, slit lamp examination including tonometry, following dilation; funduscopy and slit lamp to document lens clarity.



- <sup>8</sup> For females of childbearing potential; negative serum hCG pregnancy test must be obtained within 3 days before the first dose of study treatment. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of Cycles  $\geq 2$  and at the EoT Visit (serum hCG). Pregnancy testing may also be performed as clinically indicated during the study.
- <sup>9</sup> Response criteria include SPEP, UPEP (24-hr urine), serum and urine immunofixation, quantitative Ig levels, and serum FLC assay on C1 D1 and must be taken either on Day -1 or pre-dose on C1D1. The assessments must be repeated at the time of disease progression or suspected response in order to confirm response. Note: For patients who achieve CR or sCR, as assessed by the local lab, assessments will be confirmed by a central lab using portions of the samples collected. See the *Study Manual* for additional information.
- <sup>10</sup> Skeletal survey to be performed using x-rays per institutional guidelines. If x-rays are used, they should include a lateral radiograph of skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. If clinically appropriate, MRI, CT, or PET/CT, with tumor measurements, may be used instead of, or in addition to, x-rays. If bone lesions or plasmacytomas are observed at baseline, their number and size should be recorded in the CRF. Bone lesions and/or plasmacytomas seen at baseline using imaging should be assessed as clinically appropriate per Investigator's discretion during the study. Skeletal survey results will be read by the local laboratory.
- <sup>11</sup> If plasmacytomas are detected at baseline by PE, they should be measured and recorded, and re-assessed during the PE on Day 1 of each cycle, EoT visit, and every 3 months (if clinically appropriate) during follow-up.
- <sup>12</sup> Bone marrow aspirate:
- At Screening for Karyotyping and FISH analysis to confirm diagnosis and classify MM sub-type (required per standard of care). If sufficient sample cannot be obtained, then a bone marrow biopsy sample should be performed.
  - High-risk cytogenetic analyses and separation of CD138- and CD138+ cell fractions for subsequent genomic, transcriptomic and/or proteomic analyses (exploratory PDn study)
  - MRD analysis (exploratory PDn study) at response for selected VGPR, CR, or sCR.
- <sup>13</sup> Bone marrow biopsy:
- At time of response (as soon as feasible after SPEP, UPEP, FLC, and quantitative Ig levels are known) to confirm CR and sCR, per IMWG, by a central lab. See the *Study Manual* for additional information.
  - Two additional *optional* bone marrow core biopsies, (per Investigator's discretion), one each at baseline and after one cycle of treatment are requested and may be used for PDn exploratory studies. If sufficient sample is available, one portion of each biopsy should be fixed in 10% formalin and another portion should be fresh frozen. An archival sample taken within 30 days prior to C1D1 may be used in lieu of the baseline sample. A second sample should be obtained on C2D1 (+ 5 days) only from patients for whom a baseline sample (including archival) is also available.
- <sup>14</sup> Telephone call (or visit) with patient to evaluate supportive care medications, concomitant medications and adverse events, and to adjust supportive care as appropriate. The telephone contact with the patient must take place on C1D3 (following administration of first dose of selinexor on C1D1).
- <sup>15</sup> After treatment discontinuation, if possible, for patients who are not progressing, SPEP with serum immunofixation, UPEP (24 hr.) with urine protein immunofixation, serum FLC, and quantitative Ig levels (and physical examinations and imaging for bone lesions and plasmacytomas, if clinically appropriate) should be performed every 3 months for 1 year to assess durability of response. If these assessments cannot be performed, and for patients with PD, a telephone call will be made to the patient (or the patient's family) every 3 months for one year to inquire about the patient's survival, MM status, well-being, and information on any antineoplastic therapies utilized since discontinuation of selinexor study treatment.
- <sup>16</sup> Serious adverse events that occur after signing patient signs the ICF (including prior to first dose on C1D1) and adverse events that occur after first dose on C1D1.

## 7.2. Appendix II: Thresholds/Range Analyses for Select Laboratory, Vital Sign, and ECG Parameters

**Table 7-2 Definitions of thresholds and ranges for selected laboratory, vital signs, and ECG parameters.**

Parameter	Thresholds/Ranges	Basis or Comments
<b>Clinical Chemistry</b>		
CPK	>ULN - $\leq 2.5 \times \text{ULN}$ >2.5 - $\leq 5 \times \text{ULN}$ >5 - $\leq 10 \times \text{ULN}$ >10 $\times \text{ULN}$	CTCAE grades 1-4
Creatinine	>ULN - $\leq 1.5 \times \text{ULN}$ >1.5 - $\leq 3.0 \times \text{ULN}$ >3.0 - $\leq 6.0 \times \text{ULN}$ >6.0 $\times \text{ULN}$	CTCAE grades 1-4
Blood Urea Nitrogen	>ULN - $\leq 1.5 \times \text{ULN}$ >1.5 - $\leq 3.0 \times \text{ULN}$ >3.0 - $\leq 6.0 \times \text{ULN}$ >6.0 $\times \text{ULN}$	Same criteria as creatinine  No CTCAE
Chloride	<LLN >ULN	No CTCAE
Sodium	Hyponatremia <LLN - $\geq 130 \text{ mmol/L}$ <130 - $\geq 120 \text{ mmol/L}$ <120 $\text{mmol/L}$	CTCAE grade 1, 3, 4  (No CTCAE grade 2)
	Hypernatremia >ULN - $\leq 150 \text{ mmol/L}$ >150 $\text{mmol/L}$ - $\leq 155 \text{ mmol/L}$ >155 $\text{mmol/L}$ - $\leq 160 \text{ mmol/L}$ >160 $\text{mmol/L}$	CTCAE grade 1-4

Potassium	Hypokalemia $<LLN - \geq 3.0 \text{ mmol/L}$ $<3.0 - \geq 2.5 \text{ mmol/L}$ $<2.5 \text{ mmol/L}$	CTCAE grade 1&2, 3, 4 (Grade 1 and 2 are the same)
	Hyperkalemia $>ULN - \leq 5.5 \text{ mmol/L}$ $>5.5 - \leq 6.0 \text{ mmol/L}$ $>6.0 - \leq 7.0 \text{ mmol/L}$ $>7.0 \text{ mmol/L}$	CTCAE grade 1-4
Total Cholesterol	$>ULN - \leq 7.75 \text{ mmol/L}$ $>7.75 - \leq 10.34 \text{ mmol/L}$ $>10.34 - \leq 12.92 \text{ mmol/L}$ $>12.92 \text{ mmol/L}$	CTCAE grade 1-4
Triglycerides	$>1.71 - \leq 3.42 \text{ mmol/L}$ $>3.42 - \leq 5.7 \text{ mmol/L}$ $>5.7 - \leq 11.4 \text{ mmol/L}$ $>11.4 \text{ mmol/L}$	CTCAE grade 1-4
Glucose	Hypoglycemia $<LLN - \geq 3.0 \text{ mmol/L}$ $<3.0 - \geq 2.2 \text{ mmol/L}$ $<2.2 - \geq 1.7 \text{ mmol/L}$ $<1.7 \text{ mmol/L}$	CTCAE grade 1-4
	Hyperglycemia $>ULN - \leq 8.9 \text{ mmol/L}$ $>8.9 - \leq 13.9 \text{ mmol/L}$ $>13.9 - \leq 27.8 \text{ mmol/L}$ $>27.8 \text{ mmol/L}$	CTCAE grade 1-4
Albumin	$<LLN - \geq 30 \text{ g/L}$ $<30 - \geq 20 \text{ g/L}$ $<20 \text{ g/L}$	CTCAE grade 1-3

Amylase	>ULN - $\leq 1.5 \times \text{ULN}$ >1.5 - $\leq 2.0 \times \text{ULN}$ >2.0 - $\leq 5.0 \times \text{ULN}$ >5.0 $\times \text{ULN}$	CTCAE grade 1-4
Lipase	>ULN - $\leq 1.5 \times \text{ULN}$ >1.5 - $\leq 2.0 \times \text{ULN}$ >2.0 - $\leq 5.0 \times \text{ULN}$ >5.0 $\times \text{ULN}$	CTCAE grade 1-4
Direct bilirubin	>ULN - $\leq 1.5 \times \text{ULN}$ >1.5 - $\leq 2 \times \text{ULN}$ >2 - $\leq 3 \times \text{ULN}$ >3 - $\leq 10 \times \text{ULN}$ >10 $\times \text{ULN}$	Same Criteria as Total Bilirubin  No CTCAE  Not in DILI Guidance
GGT	>ULN - $\leq 2.5 \times \text{ULN}$ >2.5 - $\leq 5.0 \times \text{ULN}$ >5.0 - $\leq 20.0 \times \text{ULN}$ >20.0 $\times \text{ULN}$	CTCAE grade 1-4
Total protein	<LLN >ULN	No CTCAE
LDH	<LLN >ULN	No CTCAE
Calcium	Hypercalcemia  >ULN - $\leq 2.9 \text{ mmol/L}$  >2.9 - $\leq 3.1 \text{ mmol/L}$  >3.1 - $\leq 3.4 \text{ mmol/L}$  >3.4 $\text{mmol/L}$	CTCAE grade 1-4
	Hypocalcemia  <LLN - $\geq 2.0 \text{ mmol/L}$  <2.0 - $\geq 1.75 \text{ mmol/L}$  <1.75 - $\geq 1.5 \text{ mmol/L}$  <1.5 $\text{mmol/L}$	CTCAE grade 1-4
Magnesium	Hypermagnesemia  >ULN - $\leq 1.23 \text{ mmol/L}$	CTCAE grade 1, 3, 4

	$>1.23 - \leq 3.30$ mmol/L $>3.30$ mmol/L	No CTCAE grade 2
	Hypomagnesemia $<LLN - \geq 0.5$ mmol/L $<0.5 - \geq 0.4$ mmol/L $<0.4 - \geq 0.3$ mmol/L $<0.3$ mmol/L	CTCAE grade 1-4
Bicarbonate	$<LLN$ $>ULN$	No CTCAE
Inorganic phosphate	Hypophosphatemia $<LLN - \geq 0.8$ mmol/L $<0.8 - \geq 0.6$ mmol/L $<0.6 - \geq 0.3$ mmol/L $<0.3$ mmol/L	CTCAE grade 1-4
Vitamins: A, D (25-hydroxy), E, K, B12	$<LLN$	No CTCAE
LDL	$>ULN$	No CTCAE
HDL	$<LLN$	No CTCAE
ALT	$>ULN - \leq 3$ xULN $>3 - \leq 5$ xULN $>5 - \leq 8$ xULN $>8 - \leq 20.0$ xULN $>20.0$ x ULN	Per FDA DILI Guidance Jul 2009 and CTCAE
AST	$>ULN - \leq 3$ xULN $>3 - \leq 5$ xULN $>5 - \leq 8$ xULN $>8 - \leq 20.0$ xULN $>20.0$ x ULN	FDA DILI Guidance and CTCAE
ALT or AST	ALT $>3$ xULN or AST $>3$ xULN	FDA DILI Guidance

Alkaline Phosphatase	>ULN - $\leq 1.5 \times \text{ULN}$ >1.5 - $\leq 2.5 \times \text{ULN}$ >2.5 - $\leq 5.0 \times \text{ULN}$ >5.0 - $\leq 20.0 \times \text{ULN}$ >20.0 $\times \text{ULN}$	FDA DILI Guidance and CTCAE
Total Bilirubin	>ULN - $\leq 1.5 \times \text{ULN}$ >1.5 - $\leq 2 \times \text{ULN}$ >2 - $\leq 3 \times \text{ULN}$ >3 - $\leq 10 \times \text{ULN}$ >10 $\times \text{ULN}$	FDA DILI Guidance and CTCAE
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2xULN	FDA DILI Guidance Jul 2009
<b>Hematology</b>		
WBC	WBC decreased  <LLN - $\geq 3.0 \times 10^9 / \text{L}$  <3.0 - $\geq 2.0 \times 10^9 / \text{L}$  <2.0 - $\geq 1.0 \times 10^9 / \text{L}$  <1.0 $\times 10^9 / \text{L}$	CTCAE grade 1-4
	Leukocytosis >100 $\times 10^9 / \text{L}$	CTCAE grade 3 (only Grade available)
Lymphocytes	Lymphocyte decreased  <LLN - $\geq 0.8 \times 10^9 / \text{L}$  <0.8 - $\geq 0.5 \times 10^9 / \text{L}$  <0.5 - $\geq 0.2 \times 10^9 / \text{L}$  <0.2 $\times 10^9 / \text{L}$	CTCAE grade 1-4
	Lymphocyte increased >4 - $\leq 20 \times 10^9 / \text{L}$ >20 $\times 10^9 / \text{L}$	CTCAE grade 2, 3 (only Grades available)
Neutrophils	Neutrophil decreased	CTCAE grade 1-4

	$<LLN - \geq 1.5 \times 10^9 /L$ $<1.5 - \geq 1.0 \times 10^9 /L$ $<1.0 - \geq 0.5 \times 10^9 /L$ $<0.5 \times 10^9 /L$	
Monocytes	$>ULN$	No CTCAE
Basophils	$>ULN$	No CTCAE
Eosinophils	$>ULN$	No CTCAE
Hemoglobin	Hgb decreased (anemia) $<LLN - \geq 100 \text{ g/L}$ $<100 - \geq 80 \text{ g/L}$ $< 80 \text{ g/L}$	CTCAE grade 1-3
	Hgb increased $>ULN - \leq 20 \text{ g/L above ULN}$ $>20 \text{ g/L above ULN} - \leq 40 \text{ g/L above ULN}$ $>40 \text{ g/L above ULN}$	CTCAE grade 1-3
RBC	$<LLN$ $>ULN$	No CTCAE
Platelets	Platelet decreased $<LLN - \geq 75.0 \times 10^9 /L$ $<75.0 - \geq 50.0 \times 10^9 /L$ $<50.0 - \geq 25.0 \times 10^9 /L$ $<25.0 \times 10^9 /L$	CTCAE grade 1-4
	Platelet increased $>ULN$	No CTCAE available

Mean corpuscular hemoglobin	<LLN >ULN	No CTCAE
Mean corpuscular hemoglobin concentration	<LLN >ULN	No CTCAE
Mean corpuscular volume	<LLN >ULN	No CTCAE
Reticulocytes	<LLN >ULN	No CTCAE
<b>Coagulation</b>		
Activated partial thromboplastin time (PTT)	>ULN - $\leq 1.5 \times \text{ULN}$ >1.5 - $\leq 2.5 \times \text{ULN}$ >2.5 x ULN	CTCAE grade 1-3
Prothrombin time (PT) International Normalized Ratio (INR)	>ULN - $\leq 1.5 \times \text{ULN}$ >1.5 - $\leq 2.5 \times \text{ULN}$ >2.5 x ULN	CTCAE grade 1-3
<b>ECGs</b>		
HR	Bradycardia  <50 bpm Decrease from baseline $\geq 10$ bpm Decrease from baseline $\geq 20$ bpm <50 bpm and decrease from baseline $\geq 10$ bpm <50 bpm and decrease from baseline $\geq 20$ bpm	Per HV grade 2, 3, plus shift change
	Tachycardia  >120 bpm Increase from baseline $\geq 20$ bpm >120 bpm and increase from baseline $\geq 20$ bpm	Per HV grade 1, 2, 3, plus shift change
PR	$\geq 240$ ms $\geq 200$ ms and increase from baseline $\geq 40$ ms	



	$\geq 200$ ms and increase from baseline $\geq 100$ ms	
QRS	$>120$ ms Increase from baseline $\geq 20$ ms Increase from baseline $\geq 40$ ms	
QTc	$>450$ ms (Male) $>470$ ms (Female) $\geq 500$ ms Increase from baseline $>10$ ms Increase from baseline $>30$ ms Increase from baseline $>60$ ms	
<b>Vital Signs</b>		
HR	Same PCS as above in ECG category	
SBP	SBP increased $>140$ mmHg $>160$ mmHg $>10$ mmHg increase from baseline $>20$ mmHg increase from baseline  $>160$ mmHg & $>10$ mmHg increase from baseline  $>160$ mmHg & $>20$ mmHg increase from baseline	
	SBP decrease  $<100$ mmHg  $>10$ mmHg decrease from baseline $>20$ mmHg decrease from baseline	Per HV grade 1, 3, plus shift change

	<p>&lt;100 mmHg and &gt;10 mmHg decrease from baseline</p> <p>&lt;100 mmHg and &gt;20 mmHg decrease from baseline</p>	
DBP	<p>DBP increased</p> <p>&gt;90 mmHg</p> <p>&gt;100 mmHg</p> <p>&gt;5 mmHg increase from baseline</p> <p>&gt;10 mmHg increase from baseline</p> <p>&gt;100 mmHg and &gt;5 mmHg increase from baseline</p> <p>&gt;100 mmHg and &gt;10 mmHg increase from baseline</p>	
	<p>DBP decreased</p> <p>&lt;60 mmHg</p> <p>&gt;5 mmHg decrease from baseline</p> <p>&gt;10 mmHg decrease from baseline</p> <p>&lt;60 mmHg and &gt;5 mmHg decrease from baseline</p> <p>&lt;60 mmHg and &gt;10 mmHg decrease from baseline</p>	
Weight	<p>Weight gain</p> <p>≥5 % increase from baseline</p> <p>≥10 % increase from baseline</p> <p>≥ 20% increase from baseline</p>	CTCAE grade 1-3
	<p>Weight loss</p> <p>≥5 % decrease from baseline</p> <p>≥10 % decrease from baseline</p> <p>≥ 20% decrease from baseline</p>	CTCAE grade 1-3

## STATISTICAL ANALYSIS PLAN

### Protocol KCP-330-012


#### **A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) Plus Low-Dose Dexamethasone (Sd) in Patients with Multiple Myeloma Previously Treated with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib, and Daratumumab, and Refractory to Prior Treatment with Glucocorticoids, an Immunomodulatory Agent, a Proteasome Inhibitor, and the anti-CD38 mAb Daratumumab**

<b>Protocol Version:</b>	<b>5.0</b>
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<b>Date:</b>	<b>9 May 2018</b>
<b>Author:</b>	<b>Lingling Li, PhD</b>





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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition	Abbreviation	Definition
AE	adverse event	mITT	modified intent-to-treat
ALT	alanine transaminase (SGPT)	MM	multiple myeloma
aPTT	activated partial thromboplastin time	MR	minimal response
AST	aspartate transaminase (SGOT)	MRD	minimal residual disease
ATC	Anatomic Therapeutic Class	NCI	National Cancer Institute
Bpm	beats per minute	OR	odds ratio
BSA	body surface area	ORR	overall response rate
BUN	blood urea nitrogen	OS	overall survival
C1D1	Cycle 1 Day 1	PD	progressive disease
CBR	clinical benefit rate	PDn	pharmacodynamic
CI	confidence interval	PFS	progression free survival
CR	complete response	PI	proteasome inhibitor
CSR	clinical study report	PK	pharmacokinetic
CTCAE	Common Terminology Criteria for Adverse Events	PP	per protocol
DCR	disease control rate	PR	partial response
DOR	duration of response	PT	preferred term
ECG	electrocardiogram	QoL	quality of life
ECOG	Eastern Cooperative Oncology Group	QRS	the portion of an electrocardiogram comprising the Q, R, and S waves, together representing ventricular depolarization
eCRF	electronic case report form	QTcB	QT interval corrected by Bazett's formula
EDTA	ethylenediaminetetraacetic acid	QTcF	QT interval corrected by Fridericia's formula
EFS	event-free survival	SAE	serious adverse event
EoS	eosinophil count - absolute	SAP	statistical analysis plan
EoT	End of Treatment	SAS	Statistical Analysis System
ETDRS	Early Treatment Diabetic Retinopathy Study	sCR	stringent complete response
FACT-G	Functional Assessment of Cancer Therapy – General	SD	stable disease
FACT-MM	Functional Assessment of Cancer Therapy – Multiple Myeloma	Sd	selinexor 80 mg plus dexamethasone 20 mg ("low-dose" dexamethasone)
FISH	fluorescent in situ hybridization	SI	International System of Units
FLC	free light chain	SOC	system organ class
GGT	gamma-glutamyl transferase	SPEP	serum protein electrophoresis
HCO3	bicarbonate	TEAE	treatment-emergent adverse event
Hgb	hemoglobin	TOI	trial outcomes index
IMiD	immunomodulatory drug	TSH	thyroid stimulating hormone
IMWG	International Myeloma Working Group	TTP	time to progression
INR	international normalization ratio	ULN	upper limit of normal
IRC	Independent Review Committee	UPEP	urine protein electrophoresis
ISS	International Staging System	VGPR	very good partial response
ITT	intent-to-treat	WBC	white blood cell
LDH	lactate dehydrogenase	WHO	World Health Organization
LLN	lower limits of normal	WHO DDE	World Health Organization Drug Dictionary Enhanced
MedDRA	Medical Dictionary for Regulatory Activities	XPO1	exportin 1
mg	Milligram		

## 1. OVERVIEW AND INVESTIGATIONAL PLAN

### 1.1. STUDY DESIGN

KCP-330-012 is a Phase 2b, single-arm, open-label, multicenter study of Sd (selinexor 80 mg plus dexamethasone 20 mg), both dosed twice weekly, for each week of a four-week cycle, in patients with multiple myeloma (MM) previously treated with alkylating agents, glucocorticoids, lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, at least one immunomodulatory agent (IMiD), at least one proteasome inhibitor (PI), and the anti-CD38 mAb daratumumab (i.e., penta-refractory MM). Note: refractory is defined as  $\leq 25\%$  response to therapy, progression during the previously described therapies, or progression within 60 days after completion of the therapy (per International Myeloma Working Group [IMWG] criteria 2016).

This study consists of two parts and will enroll approximately 210 patients overall. Part 1 (protocol V1.0-3.0) enrolled patients with both quad-refractory MM (i.e., previously treated with alkylating agents, glucocorticoids, lenalidomide, pomalidomide, bortezomib, carfilzomib, but not an anti-CD38 mAb, and refractory to prior treatment with glucocorticoids, at least one IMiD, and at least one PI) along with patients that had quad-refractory MM and whose disease was refractory to an anti-CD38 monoclonal antibody (i.e., penta-refractory MM). Part 2 (protocol V $\geq$ 4.0) will enroll patients with penta-refractory MM only, and refractoriness to prior treatment with daratumumab (the only currently FDA approved anti-CD38 monoclonal antibody) is required.

The population for the primary efficacy analysis will contain only patients with penta-refractory MM enrolled in Part 2. Efficacy results for patients with quad-refractory MM and patients with penta-refractory MM enrolled in Part 1 will be analyzed separately. Safety analyses will be performed on the Part 2 patients with penta-refractory MM, the overall safety population of patients who received any amount of study treatment, presented together as well as separately by study part.

Patients receive oral selinexor 80 mg plus dexamethasone 20 mg (Sd), both dosed twice weekly, for each week of four-week cycles. Patients will receive treatment until progressive disease (PD), death, toxicity that cannot be managed by standard care, or withdrawal, whichever occurs first.

In select cases (e.g., for patients showing stable disease [SD] or partial response [PR] and tolerating treatment particularly well), the selinexor dose may be increased by 20 mg (up to a maximum of 100 mg per dose) after consultation with the Medical Monitor. The dose level for an individual patient may be escalated based on efficacy considerations only after a minimum of 2 cycles of study therapy. However, in no case may the dose for any patient exceed 70 mg/m<sup>2</sup>. Prior to any potential dose increase, the BSA for the patient will be calculated and an individual patient's dose may not be increased if it would result in a dose  $> 70$  mg/m<sup>2</sup>.

Patient response at each time point will be assessed centrally by an Independent Review Committee (IRC) according to the IMWG response criteria ([Kumar 2016](#)) for MM. In Part 2, MM-specific assessments (i.e., serum protein electrophoresis [SPEP], urine protein electrophoresis [UPEP], serum/urine immunofixation, quantitative Ig levels, serum free light chain [FLC], and bone marrow aspirate) must be confirmed by a central laboratory to confirm

complete response (CR) or stringent complete response (sCR), per IMWG consensus criteria. Additional information is provided in the *IRC Charter* and *Study Manual*.

Patients may decide to discontinue study treatment for any reason. Patients who elect to discontinue study treatment should be encouraged to continue in the study so that follow-up information on disease progression, other antineoplastic therapy, symptoms and survival status may be obtained. However, patients may elect to withdraw consent and decline further participation in the trial at any time. The Investigator may remove a patient from study treatment using criteria described in [Section 10.2 of Protocol V5.0](#).

The Investigator must determine the primary reason for a patient's discontinuation of study treatment and record this information on the electronic case report form (eCRF). Patients who are prematurely withdrawn from study treatment are not eligible to re-initiate study treatment on this protocol at a later date.

## 1.2. OBJECTIVES

### 1.2.1. Primary Objectives

Evaluate the efficacy (overall response rate [ORR] based on IRC assessment) for treatment with selinexor 80 mg plus low-dose dexamethasone (20 mg) (Sd) twice weekly (four-week cycles) in patients with penta-refractory MM previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab; and refractory to prior treatment with glucocorticoids, an IMiD, a PI, and the anti-CD38 mAb daratumumab.

ORR will include patients who experience PR, very good partial response (VGPR), CR, or sCR, based on IMWG response criteria ([Kumar 2016](#)). The ORR for patients with penta-refractory MM in Part 2 will be compared to a minimal threshold level of 10%.

### 1.2.2. Secondary Objectives

The following endpoints will be analyzed separately for (a) Part 1 patients with quad-refractory MM, (b) Part 1 patients with penta-refractory MM, and (c) Part 2 patients with penta-refractory MM. Additionally, analyses of safety and tolerability will be performed on the overall population of patients from Parts 1 and 2 who received at least one dose of study treatment.

- Duration of response (DOR) = Duration from first observation of at least PR to time of PD, or death due to disease progression, whichever occurs first. DOR will be censored for death due to any causes other than disease progression.
- Clinical Benefit Rate (CBR = sCR + CR + VGPR + PR + minimal response [MR]), and duration of clinical benefit (Duration from first observation of at least MR to time of PD, or death due to disease progression, whichever occurs first. Duration of clinical benefit will be censored for death due to any cause other than disease progression.
- Disease Control Rate (DCR = CBR + SD [for a minimum of 12 weeks])
- Progression Free Survival (PFS = Duration from start of study treatment to PD or death [regardless of cause], whichever comes first)
- Time to Progression (TTP = Duration from start of study treatment to time of PD) obtained with selinexor plus dexamethasone vs. TTP on most recent prior therapy

- Time to Next Treatment (TTNT = Duration from start of study treatment to start of next anti-MM treatment or death due to disease progression, whichever occurs first)
- Overall Survival (OS = Duration from start of study treatment to death)
- Quality of Life (QoL) using the Functional Assessment of Cancer Therapy - Multiple Myeloma (FACT-MM)
- Safety and tolerability using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v 4.03.
- Describe the Pharmacokinetics (PK) properties of selinexor in this patient population (Part 1 only)

### 1.2.3. Exploratory Objectives

The following endpoints will be analyzed for Part 2 patients with penta-refractory MM:

- ORR and TTNT for the patient's last treatment regimen vs. for the study treatment
- ORR, DOR, PFS, and OS in patients with Revised International Staging System (R-ISS) stage I, II, and III respectively. R-ISS stage is defined as follows:
  - A patient is classified as R-ISS stage I if the patient had baseline serum  $\beta_2$ -microglobulin level  $< 3.5$  mg/L and baseline serum albumin level  $\geq 3.5$  g/dL, had no high-risk chromosomal abnormalities (del (17p)/p53, t(14; 16), or t(4; 14)), and had normal lactate dehydrogenase (LDH) at baseline (lower than or equal to upper limit normal). Refer to [Section 2.5](#) for the definition of baseline measurement.
  - A patient is classified as R-ISS stage III if the patient had serum  $\beta_2$ -microglobulin level  $> 5.5$  mg/L at baseline, and either have high-risk chromosomal abnormalities [del (17p)/p53, t(14; 16), or t(4; 14)] or had high LDH level (above upper limit normal) at baseline.
  - A patient is classified as R-ISS II if the patient was not classified as R-ISS stage I or III.
- Minimal residual disease (MRD) in patients who achieve CR, and sCR, and selected patients who achieve VGPR.
- Correlational studies to evaluate response to treatment with selinexor as related to:
  - Cytogenetic and fluorescent *in situ* hybridization (FISH) prognostic markers, including p53 abnormalities and chromosomal aberrations (e.g., del 17p, t(4;14), t(14;16), del 13) and other MM cytogenetic classifications
  - R-ISS stage (I vs. II vs. III)
  - Time since initial diagnosis of active myeloma
  - Lytic lesions as assessed by skeletal survey (or similar bone imaging)

Chromosomal abnormalities are determined by the FISH test. If adequate test results from a central laboratory are available, such results will be used to determine the chromosomal

abnormality status; otherwise, test results from local site's laboratory will be used. If local laboratory results are not available either, FISH results from initial diagnosis (Disease History eCRF page) will be used if available. In the absence of test results indicating abnormality, a patient will be classified as normal for the corresponding mutation. Please refer to Lab Manual for details on the central laboratories and sampling and testing procedures.

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data in order to answer the study objectives. Populations for analysis, data handling rules, and statistical methods are provided. This SAP does not include endpoints and methods to be used in the analysis of PK data; these will be included in a separate plan.

### 1.3. DETERMINATION OF SAMPLE SIZE

The sample size for this study addresses the primary study objective of evaluating the clinical effect of Sd in patients with penta-refractory MM by reference to a minimal threshold level for ORR, set to 0.10 (10%). Note that the original sample size estimation for the study in Part 1 was based on clinical assumptions for patients with quad-refractory MM, and the assumptions have been updated for patients with penta-refractory MM.

Based on preliminary evidence from Part 1 of this study, it is believed that selinexor plus dexamethasone may exhibit substantial efficacy; therefore, the statistical test associated with the comparison to the threshold will maintain a Type I error rate of 0.025, 1-sided.

For the primary efficacy analysis, a sample size of 122 patients with penta-refractory MM will allow a 1-sided test at  $\alpha=0.025$  to detect an ORR of  $\geq 0.20$  against the threshold ORR of 0.10, with 90% power.

Overall, a total of ~210 patients will be enrolled, including 122 enrolled patients with penta-refractory MM (Part 2; Versions  $\geq 4.0$ ) for the primary analysis and 79 previously enrolled patients in Part 1 (78 patients with measurable disease at baseline, 30 patients with penta-refractory MM and 48 patients with quad-refractory MM enrolled under Versions  $<4.0$ ) for additional secondary and exploratory analyses.

### 1.4. STUDY PLAN

For each patient that signs the informed consent, the study consists of:

- Screening/baseline visit: occurs within 21 days prior to receiving the 1<sup>st</sup> dose of study treatment
- Treatment period: expected to be up to 12 months, but there is no maximum treatment duration. Patients will be treated until disease progression, death, toxicity that cannot be managed by standard care, or withdrawal from study, whichever occurs first
- Follow-up period: up to 12 months after last dose of study treatment, patients will be contacted approximately every 3 months for durability of response and survival follow-up

The End of Study (EoS) will occur when all patients have completed the 12-month follow-up period (i.e., when the last patient has expired, been followed for 12 months after last dose of study treatment, been lost to follow-up, or has withdrawn consent, whichever occurs first).

Please refer to [Table 7-1](#) for detailed schedule of assessment and study activities.

## 1.5. INTERIM ANALYSIS

No interim analysis is planned for this study.

## 1.6. DATABASE LOCK

The primary analysis will be performed after all patients have completed the Cycle 2 MM Assessments, and will include a formal snapshot of database and analyses of efficacy, safety, and PK data. A clinical study report (CSR) will be prepared after the primary analysis. The data cut date for IRC-based MM response assessment may be later than the data cut date for other data points. All data points presented to IRC members for their assessment have been source verified.

At the time of the database snapshot for the primary analysis, the median DOR estimate may not be estimable with limited follow-up time. Therefore, an efficacy update on ORR and DOR among the Part 2 patients with penta-refractory MM will be provided before the submission of the New Drug Application (NDA) package.

The final analysis will be performed at the end of the study after all patients have completed the 12-month follow-up period (i.e., when the last patient has expired, been followed for 12 months after last dose of study treatment, been lost to follow-up, or has withdrawn consent, whichever occurs first). There will be a formal database lock and analyses of efficacy and safety data. A final CSR will be prepared summarizing the results from the full analysis.

## 1.7. MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

The current SAP is based on Protocol v5.0. The following modifications were made to the statistical section of protocol.

### Analysis Populations

- Additional analysis populations for efficacy endpoints and additional safety populations ([Sections 3.1.1, 3.1.2, and 3.1.3](#)) are defined to present data in a comprehensive manner.
- The definition of the modified intent-to-treatment (mITT) population is revised to include patients who did not meet all eligibility criteria but received Sponsor waiver to participate in the study. Waivers are not granted to patients who do not meet key eligibility criteria such as required prior therapies and measurable disease at baseline.
- The definition of the per-protocol population is revised ([Section 3.1.1](#)). The requirement of having completed at least one cycle of treatment is removed. Instead, patients are required to have at least one adequate post-baseline response assessment unless they died or withdrew from the study before that. Moreover, patients are required to have a compliance rate of at least 70% of selinexor instead of 80%.

### Secondary Efficacy Endpoints

- The censoring rules for the secondary endpoints of duration of clinical benefits is revised to follow the TTP rule, such that it is consistent with the censoring rule for duration of response.
- The endpoint of duration of disease control is removed.



- The secondary endpoint of TTNT is added.

### Subgroup Analysis

- Subgroup analysis by R-ISS stage (I vs. II vs. III), region (US vs. non-US), and FLC MM patient (yes vs. no) respectively are added to explore potential effect modification by these factors.

### Exploratory Objective

- The R-ISS stage is used instead of the original ISS stage as the former also considers high risk chromosomal abnormalities and LDH level.
- DOR for the patient's last treatment regimen is replaced with TTNT.

## 1.8. STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

### Changes to Version 1.0

#### Section 1.2.3

- Clarified the definition of normal LDH at baseline (for R-ISS stage definition) to be "lower than or equal to upper limit normal"
- Clarified the hierarchical order of obtaining chromosomal abnormalities status: test results from central laboratories will be used if available, otherwise, test results from local laboratories will be used if available, otherwise, FISH results from initial diagnosis will be used if available.

#### Section 1.6

- The primary analysis will be performed after all patients have completed the Cycle 2 MM assessment, instead of Cycle 3 assessment
- Clarified the primary analysis will be performed based on a formal snapshot of database. In other words, data points in the database can still change after the primary analysis, but this snapshot will be frozen and will not change.

#### Section 2.6

- Revised the definition of visit windows for selected endpoints that are summarized/plotted by time points.

#### Section 2.7

- Added 2 subgroup factors on prior use of daratumumab

#### Section 3.1

- Added 2 additional analysis populations: the *All Penta-ref* population and the *Efficacy-Evaluable (EE) population*
- Removed the Part 1 six doses per cycle population and the Part 1 eight doses per cycle population

### Section 3.1.2

- Corrected that the subset of safety population from Part 2 is different from the mITT population

### Section 4.1.3

- Removed the following exploratory analyses of ORR
  - With ORR defined as the proportion of patients who achieve an unconfirmed PR or better
  - From patient's last treatment regimen, when data are available
- Added exploratory analyses of ORR by the 2 new subgroup factors on prior use of daratumumab

### Section 4.2.1.3

- Added exploratory analyses of ORR by the 2 new subgroup factors on prior use of daratumumab

### Section 4.2.4-4.2.5

- Clarified that “missing 2 or more consecutively scheduled assessments” means a gap of 65 days or longer between 2 consecutive, adequate assessments.

### Section 4.2.6.1

- Corrected the TTNT definition

### Section 4.2.7.1

- Clarified for the calculation of overall survival, patients without on-study death events will be censored at the date of discontinuation from the study, or date of last participating visit (e.g., a telephone contact with patient status being alive), or database cut date, whichever is earlier.

### Section 5.1.2.1

- Revised AE summary table

## **2. GENERAL STATISTICAL METHODS AND DATA HANDLING**

### **2.1. GENERAL ANALYSIS METHODS**

This is a single-arm, open-label study. All summary statistics will be computed and displayed among the corresponding analysis population, and by each scheduled assessment time point whenever applicable. Summary statistics for continuous variables will minimally include n, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries. Graphical displays will be provided as appropriate. Data listings will be provided as appropriate.

### **2.2. MISSING DATA HANDLING IN DATA PRESENTATION**

In general, missing baselines will not be imputed. The following approaches are default methods for missing data handling in summary tables.

- Categorical data at baseline will be summarized using counts (n) and percentages (%). Denominator will be the analysis population specified for the summary, unless otherwise specified. Missing data may be presented as a separate category.
- Continuous data: summaries will be based on observed data only.

#### **2.2.1. Handling of Computation of Treatment Duration if Study Treatment End of Treatment Date is Missing**

For the calculation of treatment duration, the date of the last dose of study treatment is equal to the date of last study treatment dosing reported on study treatment dosing form. If all the dosing dates are missing, then the duration is missing.

The last dose intake should be clearly identified on the eCRF dosing page and should not be approximated by the last returned package date.

#### **2.2.2. Handling of Missing/partial Dates for Adverse Events or Concomitant Medications**

In general, the imputation should be conservative such that onset dates should be imputed to be as early as possible and resolution dates will be imputed to be as late as possible. Impute resolution date first and then impute onset date using imputed resolution date. However, for categorization purpose, if the partial AE onset date information does not indicate whether the AE started prior to treatment or after the treatment-emergent adverse event (TEAE) period, the AE will be classified as treatment-emergent.

These data imputations are for categorization purpose or calculation of AE duration, and will not be used in listings. In data listings, an ongoing flag will be identified from the eCRF AE page.

Refer to the Karyopharm Biostatistics and Statistical Programming Rule Book for details on imputation methods.

#### **2.2.3. Handling of Missing or Partial Birth Date for Calculation of Age**

Refer to the Karyopharm Biostatistics and Statistical Programming Rule Book for details on imputation methods.

#### **2.2.4. Handling of AEs When Date and Time of First Dose of Study Treatment Are Missing**

When the date and time of the first dose of study treatment are missing, all AEs that occurred on or after signing the informed consent should be considered as TEAEs. The exposure duration should be kept as missing.

#### **2.2.5. Handling of Missing Assessment of Relationship of AEs to Study Treatment**

If the assessment of the relationship to study treatment is missing, then the relationship to study treatment in the frequency tables is considered as possibly related, but no imputation should be done at the data level or in data listings.

#### **2.2.6. Handling of Missing Severity of AEs**

If the severity is missing for one of the treatment-emergent occurrences of an AE, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a “missing” category will be added in the summary table.

### **2.3. STUDY TREATMENT DOSING DATE**

Study treatment dosing date is the date on which a patient actually received study treatment (Sd, partial or complete).

The date of first study treatment is defined as the earliest date of non-zero dose of either selinexor or dexamethasone. The date of last study treatment is defined as the latest date of non-zero dose of either selinexor or dexamethasone.

### **2.4. STUDY DAY CALCULATION**

Based on the study protocol, study Day 1 is the first study treatment dosing date. The day before Day 1 is considered Day -1; there is no Day 0.

A patient is considered as treated in a cycle if the patient received any non-zero dose of either selinexor or dexamethasone in that cycle.

Study day for a given assessment is defined as

- the assessment date – the date of first study treatment + 1 if the assessment date is on or after Day 1, or
- the assessment date – the date of first study treatment if the assessment date is before Day 1.

### **2.5. BASELINE MEASUREMENT**

In general, the baseline value is defined as latest value prior to the first dose of study treatment. In the case an assessment performed on the same date as the first dose, but it is impossible to determine the evaluation time relative to the time of taking the first dose, the evaluation time will be assumed to be following the protocol-defined schedule.

Complete myeloma disease assessments are carried out during the Screening period and on Cycle 1 Day 1 (C1D1) prior to dosing Sd. In general, values on C1D1 are used as baseline. However, the IRC will determine which values are most clinically appropriate for use as

baseline, and if values are missing on C1D1, if the values obtained during the Screening period are appropriate as baseline.

## 2.6. VISIT WINDOWS

For safety data that are summarized/plotted by time points, non-missing assessments from all scheduled and unscheduled visits will be mapped to an appropriate analysis visit using a windowing scheme. Analysis visit windows are defined in [Table 2-1](#). If there are 2 or more assessments mapped to the same analysis visit for a patient, the assessment that is closest to the target visit day will be used for analysis. If there are 2 or more assessments mapped to the same analysis visit with the same distance from the target visit day, then the latest one is selected for the analysis.

**Table 2-1 Visit Windows for Clinical Laboratory Tests and Vital Signs**

Analysis Visit Name	Target Visit Day	Study Day Range in Window
Baseline	Day 1	Prior to or on Day 1
Day 15	Day 15	Day 9 to 21
Day 29	Day 29	Day 23 to 35
Day 43	Day 43	Day 37 to 49
Day 57	Day 57	Day 51 to 63
Day 85	Day 85	Day 79 to 91
(every 28 days)		
...		
NOTE: Day 1 is the date of first study treatment dose. The visit window is +/- 6 days for post-baseline visits. Analysis visit and visit window may change for certain parameters depending on the data availability.		

## 2.7. SUBGROUPS

Subgroup analysis on selected efficacy endpoints will be conducted by

- R-ISS for MM (stage I, II, and III respectively)
- Region (US vs. non-US).
- FLC MM patient (yes vs. no), a FLC MM patient is defined as a patient without measurable disease in SPEP or UPEP, but with measurable disease in FLC, all based on baseline value.
- Prior daratumumab alone or in combination
  - ever received daratumumab in a combination therapy vs. as single agent ± dexamethasone

- received daratumumab in last line prior treatment (in combination therapy or as single agent  $\pm$  dexamethasone) vs. did not receive daratumumab in last line prior treatment

## 2.8. POOLING OF CENTERS FOR STATISTICAL ANALYSES

All participating centers in the study will be pooled together for analysis.

## 2.9. COMPUTING AND CODING STANDARDS

Activities will be performed using the following tools:

<b>Table, listing, and figure production</b>	SAS Version 9.4 or higher
<b>Coding</b>	
AEs	MedDRA Version 20.1
Medical Histories	MedDRA Version 20.1
Prior and Concomitant Medications	WHO DDE Version March 2017
<b>Grading</b>	
AEs	CTCAE Version 4.0
Labs	CTCAE Version 4.03

### 3. PATIENT INFORMATION

#### 3.1. DISPOSITION OF PATIENTS AND ANALYSIS POPULATIONS

This study consists of two parts. Part 1 (Protocol v1.0-3.0) enrolled patients with both quad-refractory MM and penta-refractory MM. Part 2 (Protocol v $\geq$ 4.0) enroll patients with penta-refractory MM only.

Patient disposition will be summarized for Part 1 and Part 2 patients separately. Patient study status will be summarized in each of the following categories:

- Screened patients, defined as any patient who has signed the informed consent form
- Patients who met study eligibility criteria (including patients who did not meet all eligibility criteria per the protocol in effect at the time of enrollment but received waiver from Sponsor) but did not receive any dose of study treatment (partial or complete)
- Patients who met study eligibility criteria (including patients who did not meet all eligibility criteria per the protocol in effect at the time of enrollment but received waiver from Sponsor) and received at least one dose of study treatment (partial or complete)
- An end-of-treatment disposition:
  - Patients who were still on treatment
  - Patients who discontinued treatment and primary reason for treatment discontinuation
- An end-of-study disposition:
  - Patients who were still on study
  - Patients who withdrew from study and primary reason for study withdrawal

##### 3.1.1. Efficacy Populations

The primary efficacy populations will only include patients from Part 2. Results for Part 1 patients will be summarized and analyzed separately.

The ***modified intent-to-treat (mITT) population*** will consist of Part 2 patients with penta-refractory MM who met all eligibility criteria (or did not meet all eligibility criteria but received waiver from Sponsor to enter the study), and received at least one dose of study treatment (partial or complete). This population will include patients who have discontinued therapy due to toxicity or PD and patients who have died from any cause, including those related to study treatment or disease. The mITT population will be used for the primary efficacy analyses.

The ***BCLPD-ref population*** will consist of patients in Part 2 who had MM *documented* to be refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab, and received at least one dose of study treatment (partial or complete).

The ***CLPD-ref population*** will consist of patients in Part 2 who had MM *documented* to be refractory to carfilzomib, lenalidomide, pomalidomide, and daratumumab, and received at least one dose of study treatment (partial or complete).

The **BCPD-ref population** will consist of patients in Part 2 who had MM *documented* to be refractory to bortezomib, carfilzomib, pomalidomide, and daratumumab, and received at least one dose of study treatment (partial or complete).

The **CPD-ref population** will consist of patients in Part 2 who had MM *documented* to be refractory to carfilzomib, pomalidomide, and daratumumab, and received at least one dose of study treatment (partial or complete). Note that this population has MM that is refractory to both second generation IMiDs (pomalidomide) and proteasome inhibitor (carfilzomib), as well as daratumumab.

The BCLPD-ref, CLPD-ref, BCPD-ref, CPD-ref populations will be used for supportive inferences concerning efficacy.

A patient is claimed to have documented refractory to a therapy if one of the following criteria is met:

- Best response on the therapy is SD or worse
- Patient progressed or relapsed during treatment
- Patient progressed or relapsed within 60 days after discontinuing this therapy.

If the date of treatment discontinuation or the date of disease progression/relapse is missing (partially or completely), unless it can be determined that one of the above criteria is met (e.g., both dates have day missing, but have the same year and month), the patient is determined to not have documented refractory.

### 3.1.2. Safety Population

The safety population will consist of all patients from Part 1 and Part 2, who have received at least one dose of study treatment (partial or complete) and have any post-baseline safety information.

Safety outputs will be presented by the following groups:

- Overall safety population
- The subset of safety population from Part 2
- The subset of safety population from Part 1

### 3.1.3. Additional Analysis Populations

Analysis of selected efficacy endpoints will be conducted in the following populations respectively:

The **All Penta-ref** population will consist of all patients from mITT (Part 2) and all Part 1 patients with penta-refractory MM who met all eligibility criteria (or did not meet all eligibility criteria but received waiver from Sponsor to enter the study), and received at least one dose of study treatment (partial or complete).

The **high-risk population** will consist of all Part 2 patients with penta-refractory MM with any of the following high-risk chromosomal abnormalities including del (17p)/p53, t(14; 16), t(4; 14), and 1q21, and received at least one dose of study treatment (partial or complete).



Chromosomal abnormalities are determined by the FISH test. If adequate test results from a central laboratory are available, such results will be used to determine the chromosomal abnormality status; otherwise, test results from the local site's laboratory will be used. If local laboratory results are not available either, FISH results from initial diagnosis (Disease History eCRF page) will be used if available. In the absence of test results indicating abnormality, a patient will be classified as normal for the corresponding mutation.

The ***Efficacy-Evaluable (EE) population*** will consist of all patients in the mITT population with at least one adequate post-baseline IRC-based MM response assessment.

The ***per-protocol (PP) population*** will consist of all patients in the mITT population who meet the following criteria:

- Have selinexor compliance  $\geq 70\%$ , see [Section 3.4.2](#) for the definition of selinexor compliance rate.
- Have at least one adequate post-baseline response assessment unless died or withdrew from study before that.

The ***Part 1 quad-ref MM population*** (Part 1 – Quad) will consist of all quad-refractory patients in Part 1 who received at least one dose of study treatment (partial or complete).

The ***Part 1 penta-ref MM population*** (Part 1 – Penta) will consist of all penta-refractory patients in Part 1 who received at least one dose of study treatment (partial or complete).

Selected safety endpoints will be summarized within the Part 1 - Quad and Part 1 - Penta, populations respectively.

## 3.2. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

In general, the baseline value is defined as latest value prior to the first dose of study treatment.

### 3.2.1. Demographic Data

Demographic variables include sex (female, male), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other), ethnicity, and age at study entry.

### 3.2.2. Prior Therapies

Prior therapies for MM will be summarized with the following variables:

- Exposure/refractory status to each individual MM treatment including lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, alkylating agent, glucocorticoid, anthracyclines, and stem cell transplant
- Refractory status to at least one IMiD, one PI, and daratumumab
- Refractory status to all five therapies including bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab
- Refractory status to all five therapies except bortezomib
- Refractory status to all five therapies except lenalidomide
- Refractory status to carfilzomib, pomalidomide, and daratumumab

- Number of prior systemic therapies (summarized as a continuous variable and as a categorical variable) and months from most recent prior systemic therapy to start of study treatment

The duration to be summarized is defined as follows.

- Months from most recent prior systemic therapy to start of study treatment will be calculated as (date of first dose of study treatment – stop date of most recent systemic therapy +1)/ (365.25/12).

### **3.2.3. Medical/surgical History**

Medical/surgical history will be summarized in the mITT population by system organ class (SOC) and preferred term (PT) using the number and percentage of patients who had at least one occurrence of a SOC and PT. The summary will be sorted by alphabetic order in SOC, and further by decreasing frequency of PT within each SOC in the mITT population. When more than one PT has the same frequency, the order of presentation will be alphabetical in PTs.

### **3.2.4. Disease History**

Disease history includes disease stage at initial diagnosis, disease stage at active myeloma, current disease stage according to ISS (or R-ISS if parameters available) for MM, and the following results at initial diagnosis:  $\beta_2$  microglobulin, albumin, immunoglobulin type, light chain type, availability of bone marrow results, % plasma cells, and availability of FISH results. Smoking history including status (Never used, Current, Former), and frequency when applicable will also be recorded.

### **3.2.5. Physical Examination and Vital Signs**

At screening, a full physical examination will be performed including height (without shoes) in centimeters (cm), weight (indoor clothing without shoes) in kilograms (kg), temperature, heart rate, systolic and diastolic blood pressure, and oxygen saturation. Significant findings that were present prior to the signing of informed consent must be included on the eCRF medical history page. Significant new findings, including the presence of plasmacytomas, that begin or worsen after informed consent must be recorded on the eCRF AE or Plasmacytoma page.

### **3.2.6. Eastern Cooperative Oncology Group (ECOG) Score**

The ECOG performance status (Grade 0-5) will be recorded at screening.

### **3.2.7. Analysis Methods**

Continuous data will be summarized using the number of available observations, mean, standard deviation, median, minimum, and maximum. Categorical and ordinal data will be summarized using the number and percentage of patients with the denominators for the percentages determined based on the analysis population used, unless otherwise specified. Demographics and baseline characteristics will be summarized among mITT, PP, BCLPD-ref, CLPD-ref, BCPD-ref, and CPD-ref populations respectively. P-values on demographic and baseline characteristic data will not be calculated. No specific description of the safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety analysis.

### **3.3. CONCOMITANT MEDICATIONS AND PROCEDURES**

#### **3.3.1. Concomitant Medications and Procedures**

Concomitant medications are any treatments received by the patient concomitantly with study treatment, from first dose of study treatment to last dose of study treatment + 30 days.

Concomitant medications include all medications used to mitigate AEs such as nausea, for supportive care, to treat or prevent infection, or to maintain the use of dexamethasone in combination of selinexor in this study. All concomitant medication(s) must be reported on the eCRF. Any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s), and any clinical findings, if applicable.

All medications will be coded using the WHO DDE Version March 2017.

Please refer to the Karyopharm Biostatistics and Statistical Programming Rule Book on definitions on prior and post-treatment medications.

#### **3.3.2. Analysis Methods**

Concomitant medications will be summarized according to the WHO DDE dictionary using the mITT population, by the anatomic and therapeutic class (ATC) level 2 (therapeutic level) and level 4 (generic level). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category linked to the medication. Therefore, patients may be counted several times for the same medication. The summary will be sorted by decreasing frequency in ATC level 2 and then ATC level 4 in the mITT population.

Please refer to [Section 2](#) for details on data handling rules related to computation, dates, imputation for missing dates.

### **3.4. EXTENT OF STUDY TREATMENT EXPOSURE AND COMPLIANCE**

The extent of study treatment exposure and compliance will be summarized in safety population.

#### **3.4.1. Extent of Study Treatment Exposure**

The extent of exposure for the study treatment will be assessed using the following variables:

- Duration of study treatment exposure
- Number of selinexor doses received
- Number of dexamethasone dose received
- Number and percentage of patients with a selinexor dose reduction
- Number and percentage of patients with a dexamethasone dose reduction
- Number and percentage of patients with a selinexor dose interruption
- Number and percentage of patients with a dexamethasone dose interruption
- Number and percentage of patients with study treatment discontinued

Duration of study treatment exposure is defined as the date of last study treatment - date of first study treatment + 1, regardless of unplanned intermittent discontinuation.

### 3.4.2. Compliance

Study treatment compliance will be summarized descriptively as a quantitative variable among the mITT population, calculated as

$$\frac{\text{number of study treatment doses taken}}{\text{number of study treatment doses prescribed}} \times 100.$$

A study treatment dose is considered prescribed if selinexor and/or dexamethasone is prescribed. The number and percentage of patients with study treatment compliance  $\geq 70\%$  will be provided. Note that the number of prescribed study treatment doses does not include doses missed due to treatment interruption or other reasons not related to patient choice.

Selinexor compliance is defined similarly among the mITT population as

$$\frac{\text{number of selinexor doses taken}}{\text{number of selinexor doses prescribed}} \times 100.$$

The number and percentage of patients with selinexor compliance  $\geq 70\%$  will be provided. Similarly, the number of prescribed selinexor doses does not include doses missed due to treatment interruption or other reasons not related to patient choice. Patients with selinexor compliance  $< 70\%$  will be excluded from the PP population.

## 4. EFFICACY

Patient response at each time point will be assessed centrally by an IRC according to the IMWG response criteria ([Kumar 2016](#)) for MM. Unless otherwise specified, MM response assessment refers to assessment determined by IRC. The primary endpoint (ORR) is based on these IRC assessed responses in the mITT population.

Documentation of response requires two consecutive readings of the applicable disease parameter (serum M-protein, urine M-protein, serum FLC, or quantitative immunoglobulin level), performed at any time with no minimum interval required between the two readings. The date of response or PD will be assigned to the earlier date of the two independent samples, unless PD is based on an unambiguous criterion such as a new plasmacytoma lesion.

If a patient had one PD assessment but was not subsequently confirmed, unless IRC considers the progression assessment unambiguous, it is not considered a PD ([Kumar 2016](#)).

Unless otherwise specified, efficacy analyses will use the mITT population. Analyses for the primary efficacy endpoint of ORR and the key secondary efficacy endpoints of DOR, CBR, and duration of clinical benefit will be repeated in the other efficacy populations and additional analysis populations. If relevant, selected efficacy analyses for other efficacy endpoints will be repeated in selected additional analysis populations.

### 4.1. PRIMARY EFFICACY ENDPOINT

#### 4.1.1. Definition

The primary endpoint is ORR which is defined as the proportion of patients who achieve a confirmed PR or better (i.e., PR, VGPR, CR, or sCR), as assessed by the IRC, during or after the study treatment, before documented disease progression or initiating a new MM treatment.

#### 4.1.2. Primary Analysis of ORR

For the primary analysis of superiority to the minimal threshold ORR, analysis will be performed using the 2-sided, exact 95% confidence interval (CI), calculated for the rate of ORR among the mITT population, and statistical significance will be declared if the lower bound of this interval is greater than 10%.

#### 4.1.3. Supportive Analyses of ORR

For exploratory purposes, ORR rates and CIs will also be calculated:

- Using the BCLPD-ref, CLPD-ref, BCPD-ref, CPD-ref, all penta-ref, high-risk, EE, PP, Part 1 – Quad, Part 1 – Penta, doses populations respectively
- Based on Investigator assessment
- In patients with R-ISS for MM stage I, II, and III respectively
- In US vs. non-US patients
- In FLC MM vs. non-FLC MM patients
- In patients ever received daratumumab as in combination therapy vs. as single-agent ± dexamethasone

- In patients received daratumumab in last line prior treatment vs. did not receive daratumumab in last line prior treatment

No formal hypothesis testing will be conducted to compare the ORR rates in the subgroup analysis.

## **4.2. SECONDARY EFFICACY ENDPOINTS**

Several of the secondary efficacy endpoints define durations based on either the progression free survival (PFS) status and time, or time to progression (TTP) status and time. In PFS, death with any cause is considered as an event. In TTP, only death due to disease progression is considered as an event. Please refer to [Table 4-1](#) and [Table 4-2](#) for details on censoring rules for PFS and TTP respectively.

### **4.2.1. Duration of Response (DOR)**

#### **4.2.1.1. Definition**

DOR is defined for patients with a confirmed PR or better as the duration from first observation of at least PR to time of IRC-determined PD or death due to disease progression, whichever occurs first. The censoring method for DOR is the same as the censoring method for TTP in [Table 4-2](#).

#### **4.2.1.2. Analysis Methods**

DOR will be summarized descriptively among those with a confirmed PR or better. Median DOR with 95% CI will be estimated based on the Kaplan-Meier method. The Kaplan-Meier curve for the duration of response will be provided.

#### **4.2.1.3. Supportive Analyses of DOR**

As supportive analyses, median DOR and 95% CI will be calculated:

- Using the BCLPD-ref, CLPD-ref, BCPD-ref, CPD-ref, all penta-ref, high-risk, EE, PP, Part 1 – Quad, Part 1 – Penta, populations respectively, if sufficient data exist
- In patients with R-ISS for MM stage I, II, and III respectively, if sufficient data exist
- In US vs. non-US patients, if sufficient data exist
- In FLC MM vs. non-FLC MM patients, if sufficient data exist.
- In patients ever received daratumumab as in combination therapy vs. as single-agent  $\pm$  dexamethasone, if sufficient data exist.
- In patients received daratumumab in last line prior treatment vs. did not receive daratumumab in last line prior treatment, if sufficient data exist.

### **4.2.2. Best Overall Response and Clinical Benefit Rate (CBR)**

#### **4.2.2.1. Definition**

The number and percentage of patients in the individual response categories (MR, PR, VGPR, CR, sCR) based on best response will be calculated respectively.

CBR is defined as the proportion of patients who achieve a confirmed MR or better, i.e., MR, PR, VGPR, CR, sCR. Duration of clinical benefit is defined as the duration from first observation of at least MR to time of IRC-determined PD or death due to disease progression, whichever occurs first. Responders without IRC-determined PD or death due to disease progression will be censored at the censored date for TTP.

#### **4.2.2.2. Analysis Methods**

The rate of CBR and the 2-sided, exact 95% CI will be calculated using the mITT population. Median duration of clinical benefit with 95% CI will be estimated based on the Kaplan-Meier method. The Kaplan-Meier curve for the duration of clinical benefit will be provided.

As supportive analyses, CBR rate and 95% CI will be calculated:

- Using the BCLPD-ref, CLPD-ref, BCPD-ref, CPD-ref, all penta-ref, high-risk, EE, PP, Part 1 – Quad, Part 1 – Penta, doses populations respectively.
- In patients with R-ISS for MM stage I, II, and III respectively
- In US vs. non-US patients
- In FLC MM vs. non-FLC MM patients.

Median duration of clinical benefit with 95% CI will be calculated in these analysis populations and subgroups when sufficient data exist.

#### **4.2.3. Disease Control Rate (DCR)**

##### **4.2.3.1. Definition**

DCR is defined as the proportion of patients who achieve SD for a minimum of 12 weeks, or better (i.e., SD for a minimum of 12 weeks, MR, PR, VGPR, CR, sCR).

##### **4.2.3.2. Analysis Methods**

The rate of DCR and the 2-sided, exact 95% CI will be calculated using the mITT population.

As supportive analyses, DCR rate and 95% CI will be calculated:

- Using the BCLPD-ref, CLPD-ref, BCPD-ref, and CPD-ref populations respectively, if sufficient data exist

#### **4.2.4. Progression Free Survival (PFS)**

##### **4.2.4.1. Definition**

PFS is defined as the duration from start of study treatment to time of IRC-determined PD or death from any cause, whichever occurs first. Please refer to [Table 4-1](#) for details on PFS outcome status (PFS event vs. censored) and date definition. Unless otherwise specified, PD status refers to confirmed PD or PD by unambiguous criteria based on IRC assessment. If PD is based on 2 independent samples on an applicable disease parameter, date of PD refers to the earlier date of the 2 independent samples.

#### 4.2.4.2. Analysis Methods

A duration is calculated as end date – start date + 1. For instance, if a PFS event occurs, then PFS time (in days) is defined as event date – start date of study treatment + 1. If a censoring event occurs, then PFS time is defined as the censoring date – start date of study treatment + 1.

**Table 4-1 PFS outcome and censoring definition**

Situation	Date of event or censoring	Outcome
No adequate post-baseline disease status assessment unless death occurs prior to first post-baseline assessment	Start of study treatment	Censored
Death before IRC-determined PD without a gap of 65 days or longer before death	Death date	PFS event
IRC-determined PD without a gap of 65 days or longer before progression	Date of PD	PFS event
No IRC-determined PD or death on or before <ul style="list-style-type: none"> <li>a. database cut,</li> <li>b. withdrawal of informed consent,</li> <li>c. lost to follow-up,</li> <li>d. documented treatment discontinuation</li> <li>e. start of new MM treatment, whichever occurs first</li> </ul>	Date of last adequate disease assessment prior to the earliest occurrence of the events (a. – e.) listed in the left column	Censored
No IRC-determined PD or death before a gap of 65 days or longer, which corresponds to 2 or more consecutively missed scheduled disease status assessment	Date of last adequate disease assessment prior to the gap	Censored

Median PFS with 95% CI will be estimated based on the Kaplan-Meier method. The Kaplan-Meier curve for PFS will be provided.

The following supportive analyses will be conducted:

- PFS based on Investigator assessment
- PFS in the BCLPD-ref, CLPD-ref, BCPD-ref, and CPD-ref populations respectively, if sufficient data exist



## 4.2.5. Time to Progression (TTP)

### 4.2.5.1. Definition

TTP is defined as the duration from start of study treatment to time of IRC-determined PD or death due to disease progression, whichever occurs first. Please refer to [Table 4-2](#) for details on TTP outcome status and date definition. Unless otherwise specified, PD assessment refers to assessment determined by IRC. But for the cause of death, disease progression refers to investigator assessment as specified on the eCRF death report page.

### 4.2.5.2. Analysis Methods

**Table 4-2 TTP outcome and censoring definition**

Situation	Date of event or censoring	Outcome
No adequate post-baseline disease status assessment unless death due to disease progression occurs prior to first post-baseline assessment	Start of study treatment	Censored
Death due to disease progression before IRC-determined PD without a gap of 65 days or longer before death	Death date	TTP event
IRC-determined PD without a gap of 65 days or longer before progression	Date of disease progression	TTP event
No IRC-determined PD or death due to disease progression on or before <ol style="list-style-type: none"> <li>1. Death due to reasons other than disease progression</li> <li>2. database cut,</li> <li>3. withdrawal of informed consent,</li> <li>4. lost to follow-up,</li> <li>5. documented treatment discontinuation</li> <li>6. start of new MM treatment, whichever occurs first</li> </ol>	Date of last adequate disease assessment prior to the earliest occurrence of the events (1. – 6.) listed in the left column	Censored
No IRC-determined PD or death due to disease progression before a gap of 65 days or longer, which corresponds to 2 or more consecutively missed scheduled disease status assessment	Date of last adequate disease assessment prior to the gap	Censored

Median TTP with 95% CI will be estimated based on the Kaplan-Meier method. The Kaplan-Meier curve for TTP will be provided.

The following supportive analyses will be conducted:

- TTP based on Investigator assessment
- TTP in the BCLPD-ref, CLPD-ref, BCPD-ref, and CPD-ref populations respectively, if sufficient data exist
- TTP on most recent prior therapy

Note that MM response assessment is scheduled to be conducted every 28 days. The maximum allowed gap length of 64 days is selected to correspond to 2 scheduled response assessments while allowing small deviations from target dates.

#### **4.2.6. Time to Next Treatment (TTNT)**

##### **4.2.6.1. Definition**

TTNT is defined as the duration from start of study treatment to start of next anti-MM treatment or death, whichever occurs first. For patients without an event, their follow-up time will be censored at the date of discontinuation from study, or last participating visit.

##### **4.2.6.2. Analysis Methods**

Median TTNT with 95% CI will be estimated based on the Kaplan-Meier method. The Kaplan-Meier curve for TTNT will be provided.

The following supportive analyses will be conducted:

- TTNT in the BCLPD-ref, CLPD-ref, BCPD-ref, and CPD-ref populations respectively, if sufficient data exist
- TTNT on most recent prior therapy

#### **4.2.7. Overall Survival (OS)**

##### **4.2.7.1. Definition**

OS is defined as the duration from start of study treatment to death from any cause. If death event did not occur during the follow-up period, the patient is censored at the date of discontinuation from the study, or date of last participating visit (e.g., a telephone contact with patient status being alive), or database cut date, whichever is earlier.

##### **4.2.7.2. Analysis Methods**

The proportion of patients with death event and the 2-sided, exact 95% CI will be calculated using the mITT population. Median OS time with 95% CI will be estimated based on the Kaplan-Meier method. The Kaplan-Meier curve for OS will be provided.

The following supportive OS analyses will be conducted:

- Using the BCLPD-ref, CLPD-ref, BCPD-ref, CPD-ref populations respectively
- Using the all penta-ref, high-risk, EE, PP, Part 1 – Quad, Part 1 – Penta, respectively, if sufficient data exist

- The same as in primary OS analysis except additional censoring at the start date of a new MM treatment
- In patients with R-ISS for MM stage I, II, and III respectively, if sufficient data exist
- In US vs. non-US patients, if sufficient data exist
- In FLC MM vs. non-FLC MM patients, if sufficient data exist
- In patients with a best response of confirmed PR or better
- In patients with a best response of confirmed MR or better
- In patients with a best response of confirmed MR
- In patients with a best response of SD or worse (including patients whose disease is not evaluable)

#### **4.2.8. Quality of life (QoL)**

##### **4.2.8.1. Definition**

Health-related QoL and potential for improvement over the course of the study will be assessed using the Functional Assessment of Cancer Therapy – Multiple Myeloma (FACT-MM) patient-reported outcome questionnaire that is specifically relevant to MM. This instrument combines the general version of the FACT (FACT-G) with a MM-specific subscale (14 items). The subscales for the FACT-G are Physical Well-Being (7 items), Social/Family Well-Being (7 items), Emotional Well-Being (6 items), and Functional Well-Being (7 items). The trial outcomes index (TOI; total of 41 items) will be the primary measurement of interest, comprised of the Physical and Functional subscales plus the MM-specific subscale. Each item is rated on a 5-point Likert scale, ranging from 0 (“Not at all”) to 4 (“Very much”), therefore the TOI has a score ranging from 0 to 120. The QoL assessment will be performed at Baseline (prior to first dose of study treatment), Day 1 of each cycle on or after the second, and at the Final visit.

##### **4.2.8.2. Analysis Methods**

The primary analysis for QoL will be based on the change from baseline on the TOI score at each assessment time point, which will be summarized using descriptive statistics including mean, standard deviation, median, minimum, and maximum. The total score considering all 5 subscales as well as the 5 individual subscale sums of scores will be summarized similarly. The same analysis windows as in [Table 2-1](#) will be used with the only exception that C1D15 is not considered as the questionnaire was not scheduled to administer during that visit.

The following supportive analyses will be conducted:

- In patients with a best response of confirmed PR or better
- In patients with a best response of confirmed MR or better

#### **4.3. EXPLORATORY EFFICACY ANALYSES**

##### **4.3.1. Minimal Residual Disease (MRD)**

MRD will be assessed at response for CR or sCR patients, and selected VGPR patients, by analyzing bone marrow aspiration specimens. A status of positive vs. negative will be assigned

based on the highest sensitivity of the assay. For patients whose disease is MRD positive, the level of positivity will also be provided.

The numbers and percentages of patients with MRD positive vs. negative status respectively at the time of response will be presented among those patients with a confirmed CR or sCR, as well as selected patients with a confirmed VGPR.

#### **4.3.2. Correlative Studies**

Contingent upon availability of sufficient data, multivariable logistic regression models will be fit to the mITT population to evaluate response to study treatment as related to the following factors (all evaluated at baseline except for FISH chromosomal abnormalities status which will be determined based on the process described in [Section 1.2.3](#)):

- FISH prognostic markers including p53 abnormalities and chromosomal aberrations (e.g., del 17p, t(4;14), t(14;16), del 13) and other MM cytogenetic classifications will be explored.
- Time since initial diagnosis of active myeloma
- Lytic lesions as measured by skeletal survey (or similar bone imaging,  $\leq 2$  vs. 3+)
- R-ISS stage (I vs. II vs. III)

Two response definitions will be explored:

- whether the patient achieved a confirmed response of PR or better
- whether the patient achieved a confirmed response of MR or better.

The independent variables for the logistic regression will also include age and region (US vs. non-US).

Corresponding odds ratios (ORs) with 2-sided 95% CIs, as well as the p-values indicating statistical significance will be presented.

## 5. SAFETY

Safety analyses will use the safety population with the outputs presented by the following groups:

- Overall safety population
- The subset of safety population from Part 2
- The subset of safety population from Part 1

Safety analyses will be based on the reported AEs and other safety information, such as 12-lead electrocardiogram (ECG), ophthalmic exam, clinical laboratory assessments including hematology, serum chemistry, coagulation parameters, and urinalysis, vital signs, physical examination, and pregnancy testing.

### ***Observation period***

The observation period will be divided into the following periods:

- The pre-treatment period is defined as the time from the signed informed consent date up to first dose of study treatment.
- The treatment period is defined as the time from first dose of study treatment to last dose of study treatment + 30 days inclusive.
- The post-treatment period is defined as the time beyond the treatment period.

The on-study observation period is pre-treatment, treatment, and post-treatment period.

### ***General rules***

All safety analyses will be performed using the following common rules:

- Safety data in patients who do not belong to the safety population (e.g., enrolled but did not receive any dose of study treatment, partial or complete) will be listed separately.
- The baseline value is the last available value before the first dose of study treatment.
- The analyses of the safety variables will be essentially descriptive and no systematic testing is planned.

## 5.1. ADVERSE EVENTS

### 5.1.1. Definitions

An AE is defined as any undesired medical occurrence in a patient or clinical investigation patient receiving a pharmaceutical product regardless of a causal relationship with this treatment. An AE can therefore be any unfavorable sign and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a study treatment, whether or not related to the study treatment.

### ***AE observation period***

- Pre-treatment AEs are AEs that developed or worsened or became serious from the signed informed consent up to first dose of study treatment.
- ***Treatment-emergent adverse events (TEAE)*** are defined as any AE that developed or worsened or became serious during the treatment period (time from first dose of study treatment to last dose of study treatment + 30 days inclusive); or any AE with a start date after the first dose of study treatment, and is considered related to study treatment by the Investigator. Note that any AE that was present at baseline but worsened in toxicity grade after first dose of study treatment, and is subsequently considered as related to study treatment shall be considered as TEAE.
- Post-treatment AEs are AEs that developed or worsened or became serious during post-treatment period and is not considered TEAE.

All AEs (including serious adverse events [SAEs]) will be coded to a PT and associated primary SOC using the MedDRA version 20.1.

The severity of all AEs will be graded according to the CTCAE Grading Scale. An AE with a CTCAE grade of 3 or higher is considered a severe AE. The severity of the AE is different from the seriousness of the AE which is defined below. For AEs not covered by CTCAE, the severity will be characterized as “mild,” “moderate,” or “severe” according to the following definitions:

- Mild events are usually transient and do not interfere with the patient’s daily activities.
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Severe events interrupt the patient’s usual daily activities.

### ***Serious adverse events***

A SAE is any untoward medical occurrence that occurs at any dose (including after the informed consent form is signed and prior to dosing) that:

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

SAE needs to be clearly documented on the patient’s AE form.

#### **5.1.2. Analysis Methods**

The primary focus of AE reporting will be on TEAEs. Pre- and post-treatment AEs will be described separately.

If an AE date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pre-treatment, treatment-emergent, or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment-emergent unless there is definitive information to determine it is

pre-treatment or post-treatment. Details on classification of AEs with missing or partial onset dates are provided in [Section 2.2.2](#).

AE summaries will include number (n) and percentage (%) of patients experiencing an AE. The denominator for computation of percentages is the number of patients in the corresponding population.

Unless otherwise specified, sorting order will follow the alphabetic order in SOC, and further by decreasing number of events in PTs within each SOC. When more than one PT has same number of events, the order of presentation will be alphabetical in PTs.

Multiple occurrences of the same event in the same patient will be counted only once in the tables.

Based on the entries on the eCRF AE page,

- An AE is considered potentially related to study treatment if:
  - the entry for “Relationship to selinexor” is either “Possibly Related” or “Related”, or
  - the entry for “Relationship to Dexamethasone” is either “Possibly Related” or “Related”.
- An AE is considered potentially related to selinexor if the entry for “Relationship to selinexor” is either “Possibly Related” or “Related”.
- An AE is considered potentially related to dexamethasone if the entry for “Relationship to Dexamethasone” is either “Possibly Related” or “Related”.

#### **5.1.2.1. Analysis of TEAEs**

An overview table summarizing the following will be presented:

- TEAEs
- TEAEs with CTCAE Grade 3 and 4
- Serious TEAEs
- TEAE leading to dose modification in selinexor, i.e., dose reduction or interruption in selinexor
- TEAEs leading to permanent treatment discontinuation
- TEAEs leading to death
  
- Treatment-related adverse events (TRAEs), i.e., TEAEs potentially related to either selinexor or dexamethasone
- Serious TRAEs
- TRAE leading to dose modification in selinexor, i.e., dose reduction or interruption in selinexor
- TRAEs leading to permanent treatment discontinuation
- TRAEs leading to death

TEAEs will be summarized by primary SOC and PT and will include the following categories:

- All TEAEs
- All TEAEs, by relatedness
  - TEAEs potentially related to either selinexor or dexamethasone
  - TEAEs potentially related to selinexor only
  - TEAEs potentially related to dexamethasone only
  - TEAEs not related to selinexor or dexamethasone
- All TEAEs, by maximum grade
- Grade 3 or higher TEAEs
- Grade 3 or higher TEAEs, by relatedness
  - Grade 3 or higher TEAEs potentially related to either selinexor or dexamethasone
  - Grade 3 or higher TEAEs potentially related to selinexor only
  - Grade 3 or higher TEAEs potentially related to dexamethasone only
  - Grade 3 or higher TEAEs not related to selinexor or dexamethasone
- TEAEs leading to selinexor dose reduced or drug interrupted
- TEAEs leading to dexamethasone dose reduced or drug interrupted
- Grade 3 or higher TEAEs leading to selinexor dose reduced or drug interrupted
- TEAEs leading to withdrawn from selinexor treatment
- Grade 3 or higher TEAEs leading to withdrawn from selinexor treatment

The most commonly reported (at least 10% of all patients) TEAEs will be presented by PT only and will include the following categories:

- The most commonly reported TEAEs
- The most commonly reported TEAEs potentially related to study treatment

#### **5.1.2.2. Analysis of SAEs**

Treat-emergent SAEs will be summarized by primary SOC and PT and will include the following categories:

- All treatment-emergent SAEs
- Treatment-emergent SAEs, by relatedness
  - Treatment-emergent SAEs potentially related to either selinexor or dexamethasone
  - Treatment-emergent SAEs potentially related to selinexor only



- Treatment-emergent SAEs potentially related to dexamethasone only
- Treatment-emergent SAEs not related to selinexor or dexamethasone
- Treatment-emergent SAEs leading to selinexor dose reduced or drug interrupted
- Treatment-emergent SAEs leading to dexamethasone dose reduced or drug interrupted
- Treatment-emergent SAEs leading to withdrawal from selinexor treatment

## 5.2. DEATH

The following summaries on death events will be provided:

- An overview of all death events and primary cause of death
- TEAEs leading to death (death as an outcome on the AE report page as reported by the Investigator), by primary SOC and PT
- TEAEs leading to death and are potentially related to selinexor or dexamethasone, by primary SOC and PT
- Listing of all death events

## 5.3. LABORATORY SAFETY VARIABLES

### 5.3.1. Definitions

Clinical laboratory data consists of blood analysis, including hematology, serum chemistry, coagulation parameters, and urinalysis. Clinical laboratory values in conventional units will be converted using the international system of units (SI).

Blood samples for clinical laboratory tests will be taken as specified in the study protocol. The laboratory parameters will be classified as follows:

- Hematology (blood sample: ethylenediaminetetraacetic acid [EDTA]) tests including hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count, WBC differential, red blood cell count, lymphocytes, monocytes, neutrophils, eosinophils, basophils, and platelets. WBC differential may be automated or manual as per institutional standards.
- Serum Chemistry (blood sample: serum)
  - Complete Serum Chemistry will include sodium, potassium, chloride, bicarbonate ( $\text{HCO}_3^-$ ), blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphate, magnesium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin and lactate dehydrogenase (LDH), total protein, albumin, amylase, lipase, creatine kinase and uric acid.
  - Limited Serum Chemistry will include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin and LDH, unless otherwise clinically indicated.
- Thyroid-stimulating hormone (TSH)

- Coagulation parameters will include prothrombin time, international normalization ratio (INR), and activated partial thromboplastin time (aPTT).
- Urinalysis will include appearance, color, urine bilirubin, glucose, hemoglobin, ketones, pH, protein, specific gravity, and urobilinogen. Microscopy will only be performed if clinically indicated.

### **5.3.2. Analysis of Laboratory Variables**

Whenever applicable, severity of selected clinical laboratory measures will be determined based on the CTCAE criteria. The worst toxicity grade in hematology and chemistry will be summarized by toxicity grade. Shift tables that present changes from baseline to worst on-study and baseline to last on-study values relative to CTCAE classification ranges will be presented.

For several key laboratory parameters (e.g., sodium, creatinine, platelet, hemoglobin, WBC, BUN-to-creatinine ratio, urea-to-creatinine ratio), box plots on measurements over time may be presented.

A listing of possible Hy's law cases (ALT or AST > 3 x upper limit of normal [ULN] with simultaneous total bilirubin > 2 x ULN) will be presented. The elevations of ALT/AST and total bilirubin must occur within 2 days of each other.

Thresholds/Range analyses for selected laboratory, vital signs, and ECG parameters will be conducted. Please refer to [Appendix 7.2](#) for the definitions on thresholds/ranges for selected parameters. The number and percentage of patients classified into each category based on worst values will be presented.

## **5.4. VITAL SIGNS, ECOG, AND PHYSICAL EXAMINATION VARIABLES**

Full physical examinations with vital signs are performed only during screening and end-of-treatment (EoT) visits, including height (without shoes) in centimeters (cm) [measured during screening visit only], weight (indoor clothing without shoes) in kilograms (kg), temperature, heart rate, systolic and diastolic blood pressure, and oxygen saturation.

At other visits, symptom-directed physical examinations are conducted with vital signs (temperature, heart rate, systolic and diastolic blood pressure).

An ECOG score assessment with grades 0-5 will be performed during screening, day 1 of each cycle, and the EoT visit.

Shift tables that present changes from baseline to worst on-study and last on-study for systolic blood pressure, diastolic blood pressure, and ECOG performance status values will be produced.

Abnormal vital signs results will be summarized in the threshold/range analyses as defined in [Appendix 7.2](#).

## **5.5. ELECTROCARDIOGRAM (ECG)**

Standard 12-lead ECGs will be performed during screening and EoT visits. Patients must rest for at least 5 minutes prior to the ECG recording. The Investigator will interpret the ECG using one of the following categories: normal, abnormal but not clinically significant, or abnormal and clinically significant. The following will be assessed: heart rate, rhythm, interval from start of

the Q wave to the end of the S wave (QRS), interval from the beginning of the P wave until the beginning of the QRS complex (PR Interval), interval between the start of the Q wave and the end of the T wave (QT), and QT corrected (QTc) using Bazett's formula or calculated by the Fridericia correction formula (*Bazett 1920, Fridericia 1920*). If Bazett correction is entered by the site, the Fridericia corrected QTc interval (QTcF) will be derived using the formula:  $QT/(RR^{1/3})$ , where  $RR = 60/\text{heart rate}$ .

Abnormal ECG results will be summarized in the threshold/range analyses as defined in [Appendix 7.2](#).

## 5.6. OPTHALMIC EXAM

A full ophthalmic examination will be performed during the Screening and EoT visits. Prior to dilation, best corrected visual acuity (Snellen's Equivalent based on either Snellen chart or Early Treatment Diabetic Retinopathy Study [ETDRS chart]), and slit lamp examination including tonometry will be conducted. Following dilation, fundoscopy will be conducted. Please refer to Protocol v5.0 for details on the grading of cataract if seen during the examination.

All ophthalmic examination findings will be presented in a data listing.

## 6. REFERENCES

1. DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Medicine*. 1916;17:863-871.
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3. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med*. 1987;317:1098.

## 7. APPENDICE

### 7.1. Appendix I: Schedule of Assessments

Table 7-1 Schedule of Assessments and Study Activities

Activity/Assessment	Screening	Cycle 1				Cycle 2		Cycles $\geq 3$	End-of-Treatment (EoT) Visit	Safety Follow-up Call	Durability of Response and Survival Follow-up <sup>15</sup>
	Day -21 to Day -1	Day 1	Day 3 <sup>14</sup>	Day 8	Day 15	Day 1	Day 15	Day 1	$\leq 14$ Days Post Last Dose	30 Days Post-Last Dose	Every 3 mo.
		-1 day	+1 day	$\pm 1$ day	$\pm 1$ day	$\pm 2$ days	$\pm 2$ days	$\pm 2$ days		+ 7 days	$\pm 14$ days
Informed consent <sup>1</sup>	X										
Inclusion/exclusion criteria	X										
Demographics	X										
Medical history <sup>2</sup>	X	X									
Patient height	X										
Patient weight	X	X		X	X	X	X	X	X		
Body Surface Area (BSA) <sup>3</sup>	X										
Physical examination, full including vital signs <sup>4</sup>	X								X		

Activity/Assessment	Screening	Cycle 1				Cycle 2		Cycles $\geq 3$	End-of-Treatment (EoT) Visit	Safety Follow-up Call	Durability of Response and Survival Follow-up <sup>15</sup>
	Day -21 to Day -1	Day 1	Day 3 <sup>14</sup>	Day 8	Day 15	Day 1	Day 15	Day 1	$\leq 14$ Days Post Last Dose	30 Days Post-Last Dose	Every 3 mo.
		-1 day	+1 day	$\pm 1$ day	$\pm 1$ day	$\pm 2$ days	$\pm 2$ days	$\pm 2$ days		+ 7 days	$\pm 14$ days
Physical examination, symptom-directed, including vital signs <sup>4</sup>		X		X	X	X	X	X			
ECOG <sup>5</sup>	X					X		X	X		
Echocardiogram or MUGA <sup>6</sup>	X										
12-lead ECG	X								X		
Ophthalmic exam <sup>7</sup>	X								X		
Clinical Labs											
Urinalysis <sup>5</sup>	X								X		
CBC with differential <sup>5</sup>	X				X	X	X	X	X		
TSH <sup>5</sup>	X								X		
Complete serum chemistry <sup>5</sup>	X					X		X	X		

Activity/Assessment	Screening	Cycle 1				Cycle 2		Cycles $\geq 3$	End-of-Treatment (EoT) Visit	Safety Follow-up Call	Durability of Response and Survival Follow-up <sup>15</sup>
	Day -21 to Day -1	Day 1	Day 3 <sup>14</sup>	Day 8	Day 15	Day 1	Day 15	Day 1	$\leq 14$ Days Post Last Dose	30 Days Post-Last Dose	Every 3 mo.
		-1 day	+1 day	$\pm 1$ day	$\pm 1$ day	$\pm 2$ days	$\pm 2$ days	$\pm 2$ days		+ 7 days	$\pm 14$ days
Limited serum chemistry				X	X		X				
Coagulation tests <sup>5</sup>	X								X		
Serum hCG pregnancy test <sup>8</sup>	X					X (D1 of each cycle only)		X (D1 of each cycle only)	X		
C-reactive protein	X	X				X		X	X		
Multiple Myeloma Assessments											
SPEP and serum protein immunofixation <sup>9</sup>	X	X				X		X	X		X
UPEP (24-hr urine for total protein) and urine protein immunofixation <sup>9</sup>	X	X				X		X	X		X
Quantitative Ig levels <sup>9</sup>	X	X				X		X	X		X

Activity/Assessment	Screening	Cycle 1				Cycle 2		Cycles $\geq 3$	End-of-Treatment (EoT) Visit	Safety Follow-up Call	Durability of Response and Survival Follow-up <sup>15</sup>
	Day -21 to Day -1	Day 1	Day 3 <sup>14</sup>	Day 8	Day 15	Day 1	Day 15	Day 1	$\leq 14$ Days Post Last Dose	30 Days Post-Last Dose	Every 3 mo.
		-1 day	+1 day	$\pm 1$ day	$\pm 1$ day	$\pm 2$ days	$\pm 2$ days	$\pm 2$ days		+ 7 days	$\pm 14$ days
Serum FLC <sup>9</sup>	X	X			X	X	X	X	X		X
$\beta_2$ -microglobulin	X								X		
Skeletal survey <sup>10</sup>	X					(X)		(X)	X		(X)
Plasmacytoma assessment <sup>11</sup>	X					(X)		(X)	X		(X)
Bone marrow aspirate <sup>12</sup>	X					(X)		(X)			(X)
Bone marrow core biopsy <sup>13</sup>	X					(X)					
FACT-MM questionnaire	X					X		X	X		
Study treatment dosing		Selinexor 80 mg + dexamethasone 20 mg (both twice weekly) for 4 weeks (each week) of 4-week cycles									
Adverse events <sup>16</sup>	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X		



Activity/Assessment	Screening	Cycle 1				Cycle 2		Cycles $\geq 3$	End-of-Treatment (EoT) Visit	Safety Follow-up Call	Durability of Response and Survival Follow-up <sup>15</sup>
	Day -21 to Day -1	Day 1	Day 3 <sup>14</sup>	Day 8	Day 15	Day 1	Day 15	Day 1	$\leq 14$ Days Post Last Dose	30 Days Post-Last Dose	Every 3 mo.
		-1 day	+1 day	$\pm 1$ day	$\pm 1$ day	$\pm 2$ days	$\pm 2$ days	$\pm 2$ days		+ 7 days	$\pm 14$ days
Nutritional consultation	X										
Telephone contact <sup>14</sup>			X							X	X
Antineoplastic therapy after EoT									X	X	X

(X) indicates that additional information is provided in the footnotes. Merged cells indicate that the procedure may be performed during either Screening or the C1D1 visit.

Abbreviations: BSA = body surface area; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoT = End of Treatment; Ig = immunoglobulin; MM = multiple myeloma; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; CBC = complete blood count; FLC = free light chain.

<sup>1</sup> Prior to the first study-specific measure.

<sup>2</sup> Including details of all prior anti-myeloma therapies. Includes baseline symptoms as well as a detailed history of prior cancer therapies, especially MM therapies, including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness.

<sup>3</sup> Body Surface Area (BSA) will be calculated by [Dubois 1916](#) or [Mosteller 1987](#) method during Screening and prior to any dose escalation. No patient may receive a dose of selinexor  $> 70$  mg/m<sup>2</sup>.

<sup>4</sup> Complete physical examination (PE) during Screening and EoT visit. Limited PEs during the study should be symptom directed. All PEs to include vital signs (blood pressure, pulse and body temperature).

<sup>5</sup> The following procedures may be performed at Screening or pre-dose on C1D1 and as shown in the Schedule during the study: ECOG performance assessment, echocardiogram or MUGA scan, 12-lead ECG, ophthalmic exam, urinalysis, CBC with differential, TSH, complete serum chemistry, coagulations tests, and nutritional consultation.

<sup>6</sup> Echocardiogram or MUGA scan at Screening and as clinically indicated during the study.

<sup>7</sup> A full ophthalmic examination will include, prior to dilation, best corrected visual acuity, slit lamp examination including tonometry, following dilation; funduscopy and slit lamp to document lens clarity.

- <sup>8</sup> For females of childbearing potential; negative serum hCG pregnancy test must be obtained within 3 days before the first dose of study treatment. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of Cycles  $\geq 2$  and at the EoT Visit (serum hCG). Pregnancy testing may also be performed as clinically indicated during the study.
- <sup>9</sup> Response criteria include SPEP, UPEP (24-hr urine), serum and urine immunofixation, quantitative Ig levels, and serum FLC assay on C1 D1 and must be taken either on Day -1 or pre-dose on C1D1. The assessments must be repeated at the time of disease progression or suspected response in order to confirm response. Note: For patients who achieve CR or sCR, as assessed by the local lab, assessments will be confirmed by a central lab using portions of the samples collected. See the *Study Manual* for additional information.
- <sup>10</sup> Skeletal survey to be performed using x-rays per institutional guidelines. If x-rays are used, they should include a lateral radiograph of skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. If clinically appropriate, MRI, CT, or PET/CT, with tumor measurements, may be used instead of, or in addition to, x-rays. If bone lesions or plasmacytomas are observed at baseline, their number and size should be recorded in the CRF. Bone lesions and/or plasmacytomas seen at baseline using imaging should be assessed as clinically appropriate per Investigator's discretion during the study. Skeletal survey results will be read by the local laboratory.
- <sup>11</sup> If plasmacytomas are detected at baseline by PE, they should be measured and recorded, and re-assessed during the PE on Day 1 of each cycle, EoT visit, and every 3 months (if clinically appropriate) during follow-up.
- <sup>12</sup> Bone marrow aspirate:
- a. At Screening for Karyotyping and FISH analysis to confirm diagnosis and classify MM sub-type (required per standard of care). If sufficient sample cannot be obtained, then a bone marrow biopsy sample should be performed.
  - b. High-risk cytogenetic analyses and separation of CD138- and CD138+ cell fractions for subsequent genomic, transcriptomic and/or proteomic analyses (exploratory PDn study)
  - c. MRD analysis (exploratory PDn study) at response for selected VGPR, CR, or sCR .
- <sup>13</sup> Bone marrow biopsy:
- a. At time of response (as soon as feasible after SPEP, UPEP, FLC, and quantitative Ig levels are known) to confirm CR and sCR, per IMWG, by a central lab. See the *Study Manual* for additional information.
  - b. Two additional *optional* bone marrow core biopsies, (per Investigator's discretion), one each at baseline and after one cycle of treatment are requested and may be used for PDn exploratory studies. If sufficient sample is available, one portion of each biopsy should be fixed in 10% formalin and another portion should be fresh frozen. An archival sample taken within 30 days prior to C1D1 may be used in lieu of the baseline sample. A second sample should be obtained on C2D1 (+ 5 days) only from patients for whom a baseline sample (including archival) is also available.
- <sup>14</sup> Telephone call (or visit) with patient to evaluate supportive care medications, concomitant medications and adverse events, and to adjust supportive care as appropriate. The telephone contact with the patient must take place on C1D3 (following administration of first dose of selinexor on C1D1).
- <sup>15</sup> After treatment discontinuation, if possible, for patients who are not progressing, SPEP with serum immunofixation, UPEP (24 hr.) with urine protein immunofixation, serum FLC, and quantitative Ig levels (and physical examinations and imaging for bone lesions and plasmacytomas, if clinically appropriate) should be performed every 3 months for 1 year to assess durability of response. If these assessments cannot be performed, and for patients with PD, a telephone call will be made to the patient (or the patient's family) every 3 months for one year to inquire about the patient's survival, MM status, well-being, and information on any antineoplastic therapies utilized since discontinuation of selinexor study treatment.
- <sup>16</sup> Serious adverse events that occur after signing patient signs the ICF (including prior to first dose on C1D1) and adverse events that occur after first dose on C1D1.

## 7.2. Appendix II: Thresholds/Range Analyses for Select Laboratory, Vital Sign, and ECG Parameters

**Table 7-2** Definitions of thresholds and ranges for selected laboratory, vital signs, and ECG parameters.

Parameter	Thresholds/Ranges	Basis or Comments
<b>Clinical Chemistry</b>		
CPK	>ULN - $\leq 2.5 \times \text{ULN}$ >2.5 - $\leq 5 \times \text{ULN}$ >5 - $\leq 10 \times \text{ULN}$ >10 x ULN	CTCAE grades 1-4
Creatinine	>ULN - $\leq 1.5 \times \text{ULN}$ >1.5 - $\leq 3.0 \times \text{ULN}$ >3.0 - $\leq 6.0 \times \text{ULN}$ >6.0 x ULN	CTCAE grades 1-4
Blood Urea Nitrogen	>ULN - $\leq 1.5 \times \text{ULN}$ >1.5 - $\leq 3.0 \times \text{ULN}$ >3.0 - $\leq 6.0 \times \text{ULN}$ >6.0 x ULN	Same criteria as creatinine  No CTCAE
Chloride	<LLN >ULN	No CTCAE
Sodium	Hyponatremia <LLN - $\geq 130 \text{ mmol/L}$ <130 - $\geq 120 \text{ mmol/L}$ <120 mmol/L	CTCAE grade 1, 3, 4  (No CTCAE grade 2)
	Hypernatremia >ULN - $\leq 150 \text{ mmol/L}$ >150 mmol/L - $\leq 155 \text{ mmol/L}$ >155 mmol/L - $\leq 160 \text{ mmol/L}$ >160 mmol/L	CTCAE grade 1-4

Potassium	Hypokalemia <LLN – $\geq 3.0$ mmol/L <3.0 – $\geq 2.5$ mmol/L <2.5 mmol/L	CTCAE grade 1&2, 3, 4 (Grade 1 and 2 are the same)
	Hyperkalemia >ULN – $\leq 5.5$ mmol/L >5.5 – $\leq 6.0$ mmol/L >6.0 – $\leq 7.0$ mmol/L >7.0 mmol/L	CTCAE grade 1-4
Total Cholesterol	>ULN – $\leq 7.75$ mmol/L >7.75 – $\leq 10.34$ mmol/L >10.34 – $\leq 12.92$ mmol/L >12.92 mmol/L	CTCAE grade 1-4
Triglycerides	>1.71 – $\leq 3.42$ mmol/L >3.42 – $\leq 5.7$ mmol/L >5.7 – $\leq 11.4$ mmol/L >11.4 mmol/L	CTCAE grade 1-4
Glucose	Hypoglycemia <LLN – $\geq 3.0$ mmol/L <3.0 – $\geq 2.2$ mmol/L <2.2 – $\geq 1.7$ mmol/L <1.7 mmol/L	CTCAE grade 1-4
	Hyperglycemia >ULN – $\leq 8.9$ mmol/L >8.9 – $\leq 13.9$ mmol/L >13.9 – $\leq 27.8$ mmol/L >27.8 mmol/L	CTCAE grade 1-4
Albumin	<LLN – $\geq 30$ g/L <30 – $\geq 20$ g/L <20 g/L	CTCAE grade 1-3

Amylase	>ULN - $\leq 1.5 \times \text{ULN}$ >1.5 - $\leq 2.0 \times \text{ULN}$ >2.0 - $\leq 5.0 \times \text{ULN}$ >5.0 $\times \text{ULN}$	CTCAE grade 1-4
Lipase	>ULN - $\leq 1.5 \times \text{ULN}$ >1.5 - $\leq 2.0 \times \text{ULN}$ >2.0 - $\leq 5.0 \times \text{ULN}$ >5.0 $\times \text{ULN}$	CTCAE grade 1-4
Direct bilirubin	>ULN - $\leq 1.5 \times \text{ULN}$ >1.5 - $\leq 2 \times \text{ULN}$ >2 - $\leq 3 \times \text{ULN}$ >3 - $\leq 10 \times \text{ULN}$ >10 $\times \text{ULN}$	Same Criteria as Total Bilirubin  No CTCAE  Not in DILI Guidance
GGT	>ULN - $\leq 2.5 \times \text{ULN}$ >2.5 - $\leq 5.0 \times \text{ULN}$ >5.0 - $\leq 20.0 \times \text{ULN}$ >20.0 $\times \text{ULN}$	CTCAE grade 1-4
Total protein	<LLN >ULN	No CTCAE
LDH	<LLN >ULN	No CTCAE
Calcium	Hypercalcemia  >ULN - $\leq 2.9 \text{ mmol/L}$  >2.9 - $\leq 3.1 \text{ mmol/L}$  >3.1 - $\leq 3.4 \text{ mmol/L}$  >3.4 $\text{mmol/L}$	CTCAE grade 1-4
	Hypocalcemia  <LLN - $\geq 2.0 \text{ mmol/L}$  <2.0 - $\geq 1.75 \text{ mmol/L}$  <1.75 - $\geq 1.5 \text{ mmol/L}$  <1.5 $\text{mmol/L}$	CTCAE grade 1-4
Magnesium	Hypermagnesemia  >ULN - $\leq 1.23 \text{ mmol/L}$	CTCAE grade 1, 3, 4

	$>1.23 - \leq 3.30$ mmol/L $>3.30$ mmol/L	No CTCAE grade 2
	Hypomagnesemia $<LLN - \geq 0.5$ mmol/L $<0.5 - \geq 0.4$ mmol/L $<0.4 - \geq 0.3$ mmol/L $<0.3$ mmol/L	CTCAE grade 1-4
Bicarbonate	$<LLN$ $>ULN$	No CTCAE
Inorganic phosphate	Hypophosphatemia $<LLN - \geq 0.8$ mmol/L $<0.8 - \geq 0.6$ mmol/L $<0.6 - \geq 0.3$ mmol/L $<0.3$ mmol/L	CTCAE grade 1-4
Vitamins: A, D (25-hydroxy), E, K, B12	$<LLN$	No CTCAE
LDL	$>ULN$	No CTCAE
HDL	$<LLN$	No CTCAE
ALT	$>ULN - \leq 3$ xULN $>3 - \leq 5$ xULN $>5 - \leq 8$ xULN $>8 - \leq 20.0$ xULN $>20.0$ x ULN	Per FDA DILI Guidance Jul 2009 and CTCAE
AST	$>ULN - \leq 3$ xULN $>3 - \leq 5$ xULN $>5 - \leq 8$ xULN $>8 - \leq 20.0$ xULN $>20.0$ x ULN	FDA DILI Guidance and CTCAE
ALT or AST	ALT $>3$ xULN or AST $>3$ xULN	FDA DILI Guidance

Alkaline Phosphatase	>ULN - $\leq 1.5 \times \text{ULN}$ >1.5 - $\leq 2.5 \times \text{ULN}$ >2.5 - $\leq 5.0 \times \text{ULN}$ >5.0 - $\leq 20.0 \times \text{ULN}$ >20.0 x ULN	FDA DILI Guidance and CTCAE
Total Bilirubin	>ULN - $\leq 1.5 \times \text{ULN}$ >1.5 - $\leq 2 \times \text{ULN}$ >2 - $\leq 3 \times \text{ULN}$ >3 - $\leq 10 \times \text{ULN}$ >10 x ULN	FDA DILI Guidance and CTCAE
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2xULN	FDA DILI Guidance Jul 2009
<b>Hematology</b>		
WBC	WBC decreased  <LLN - $\geq 3.0 \times 10^9 / \text{L}$ <3.0 - $\geq 2.0 \times 10^9 / \text{L}$ <2.0 - $\geq 1.0 \times 10^9 / \text{L}$ <1.0 x 10 <sup>9</sup> /L	CTCAE grade 1-4
	Leukocytosis >100 x 10 <sup>9</sup> /L	CTCAE grade 3 (only Grade available)
Lymphocytes	Lymphocyte decreased  <LLN - $\geq 0.8 \times 10^9 / \text{L}$ <0.8 - $\geq 0.5 \times 10^9 / \text{L}$ <0.5 - $\geq 0.2 \times 10^9 / \text{L}$ <0.2 x 10 <sup>9</sup> /L	CTCAE grade 1-4
	Lymphocyte increased >4 - $\leq 20 \times 10^9 / \text{L}$ >20 x 10 <sup>9</sup> /L	CTCAE grade 2, 3 (only Grades available)
Neutrophils	Neutrophil decreased  <LLN - $\geq 1.5 \times 10^9 / \text{L}$	CTCAE grade 1-4

	$<1.5 - \geq 1.0 \times 10^9 /L$ $<1.0 - \geq 0.5 \times 10^9 /L$ $<0.5 \times 10^9 /L$	
Monocytes	>ULN	No CTCAE
Basophils	>ULN	No CTCAE
Eosinophils	>ULN	No CTCAE
Hemoglobin	Hgb decreased (anemia) $<LLN - \geq 100 \text{ g/L}$ $<100 - \geq 80 \text{ g/L}$ $< 80 \text{ g/L}$	CTCAE grade 1-3
	Hgb increased $>ULN - \leq 20 \text{ g/L above ULN}$ $>20 \text{ g/L above ULN} - \leq 40 \text{ g/L above ULN}$ $>40 \text{ g/L above ULN}$	CTCAE grade 1-3
RBC	<LLN	No CTCAE
	>ULN	
Platelets	Platelet decreased $<LLN - \geq 75.0 \times 10^9 /L$ $<75.0 - \geq 50.0 \times 10^9 /L$ $<50.0 - \geq 25.0 \times 10^9 /L$ $<25.0 \times 10^9 /L$	CTCAE grade 1-4
	Platelet increased $>ULN$	No CTCAE available
Mean corpuscular hemoglobin	<LLN >ULN	No CTCAE



Mean corpuscular hemoglobin concentration	<LLN >ULN	No CTCAE
Mean corpuscular volume	<LLN >ULN	No CTCAE
Reticulocytes	<LLN >ULN	No CTCAE
<b>Coagulation</b>		
Activated partial thromboplastin time (PTT)	>ULN - $\leq 1.5 \times \text{ULN}$ >1.5 - $\leq 2.5 \times \text{ULN}$ >2.5 x ULN	CTCAE grade 1-3
Prothrombin time (PT) International Normalized Ratio (INR)	>ULN - $\leq 1.5 \times \text{ULN}$ >1.5 - $\leq 2.5 \times \text{ULN}$ >2.5 x ULN	CTCAE grade 1-3
<b>ECGs</b>		
HR	Bradycardia  <50 bpm Decrease from baseline $\geq 10$ bpm Decrease from baseline $\geq 20$ bpm <50 bpm and decrease from baseline $\geq 10$ bpm <50 bpm and decrease from baseline $\geq 20$ bpm	Per HV grade 2, 3, plus shift change
	Tachycardia  >120 bpm Increase from baseline $\geq 20$ bpm >120 bpm and increase from baseline $\geq 20$ bpm	Per HV grade 1, 2, 3, plus shift change
PR	$\geq 240$ ms $\geq 200$ ms and increase from baseline $\geq 40$ ms $\geq 200$ ms and increase from baseline $\geq 100$ ms	

QRS	<p>&gt;120 ms</p> <p>Increase from baseline <math>\geq 20</math> ms</p> <p>Increase from baseline <math>\geq 40</math> ms</p>	
QTc	<p>&gt;450 ms (Male)</p> <p>&gt;470 ms (Female)</p> <p><math>\geq 500</math> ms</p> <p>Increase from baseline &gt;10 ms</p> <p>Increase from baseline &gt;30 ms</p> <p>Increase from baseline &gt;60 ms</p>	
<b>Vital Signs</b>		
HR	Same PCS as above in ECG category	
SBP	<p>SBP increased</p> <p>&gt;140 mmHg</p> <p>&gt;160 mmHg</p> <p>&gt;10 mmHg increase from baseline</p> <p>&gt;20 mmHg increase from baseline</p> <p>&gt;160 mmHg &amp; &gt;10 mmHg increase from baseline</p> <p>&gt;160 mmHg &amp; &gt;20 mmHg increase from baseline</p>	
	<p>SBP decrease</p> <p>&lt;100 mmHg</p> <p>&gt;10 mmHg decrease from baseline</p> <p>&gt;20 mmHg decrease from baseline</p> <p>&lt;100 mmHg and &gt;10 mmHg decrease from baseline</p>	Per HV grade 1, 3, plus shift change

	<100 mmHg and >20 mmHg decrease from baseline	
DBP	DBP increased  >90 mmHg >100 mmHg >5 mmHg increase from baseline >10 mmHg increase from baseline  >100 mmHg and >5 mmHg increase from baseline >100 mmHg and >10 mmHg increase from baseline	
	DBP decreased <60 mmHg >5 mmHg decrease from baseline >10 mmHg decrease from baseline <60 mmHg and >5 mmHg decrease from baseline <60 mmHg and >10 mmHg decrease from baseline	
Weight	Weight gain ≥5 % increase from baseline ≥10 % increase from baseline ≥ 20% increase from baseline	CTCAE grade 1-3
	Weight loss ≥5 % decrease from baseline ≥10 % decrease from baseline ≥ 20% decrease from baseline	CTCAE grade 1-3