CLINICAL STUDY PROTOCOL

KCP-330-023

A PHASE 3 RANDOMIZED, CONTROLLED, OPEN-LABEL STUDY OF SELINEXOR, BORTEZOMIB, AND DEXAMETHASONE (SVD) VERSUS BORTEZOMIB AND DEXAMETHASONE (VD) IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM)

Study Name: BOSTON: Bortezomib, Selinexor, and Dexamethasone in Patients with Multiple Myeloma

Study Number:	KCP-330-023
Study Phase:	3
Investigational Product:	Selinexor (KPT-330)
EudraCT Number:	2016-003957-14
Indication:	Relapsed or refractory multiple myeloma (RRMM)
Sponsor:	Karyopharm Therapeutics Inc. 85 Wells Avenue Newton, MA 02459 USA Tel. + (617) 658-0600
Protocol Date and Version:	18 November 2016, Version 1.0 22 February 2017, Version 2.0 (Amendment 1) 06 April 2017, Version 3.0 (Amendment 2) 17 August 2018, Version 4.0 (Amendment 3)

CONDUCT

In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.

PROTOCOL APPROVAL SIGNATURE PAGE

SPONSOR: KARYOPHARM THERAPEUTICS INC.

I have read and understand the contents of this clinical protocol for Study KCP-330-023 dated 17 August 2018 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:

PPD

17 August 2018

PPD **MD** **Date**

PPD

Karyopharm Therapeutics Inc.

17 August 2018

PPD **PhD, MBA** **Date**

PPD

Karyopharm Therapeutics Inc.

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17 August 2018

PPD **MD** — **Date**

PPD

Karyopharm Therapeutics Inc.

PPD

17 August 2018

PPD **PhD, MBA** — **Date**

PPD

Karyopharm Therapeutics Inc.

INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Study KCP-330-023 dated 17 August 2018 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 Practice, ICH E6, and applicable FDA regulatory requirements.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Institution

_____

Date

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Definitions of Terms

Abbreviation or Specialist Term	Explanation
5-HT3	5-hydroxytryptamine
ACS	American Cancer Society
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOA	American Optometric Association
API	active pharmaceutical ingredient
ASCT	autologous stem-cell transplantation
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
$AUC_{0-\infty}$	area under the concentration versus time curve from the time of dosing extrapolated to infinity
BIW	twice weekly
bort	bortezomib
BP	blood pressure
BSA	body surface area
C	visit for in-clinic dosing only
CA	chromosomal abnormalities
CBC	complete blood count
CI	confidence interval
CIPN20	Chemotherapy-induced Peripheral Neuropathy
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CR	complete response
CRAB features	calcium elevation, renal failure, anemia, lytic bone lesions
CrCl	creatinine clearance
CRM1	chromosome region maintenance protein 1
CSR	clinical study report

Abbreviation or Specialist Term	Explanation
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CXDX (eg, C1D1)	Cycle X Day X (eg, Cycle 1 Day 1)
D	day
Dex	dexamethasone
DOR	duration of response
DSMB	Data Safety Monitoring Board
eCRF	electronic case report form
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EoT	end of treatment
CCI	[redacted]
FACS	fluorescence activated cell sorting
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FISH	fluorescence in situ hybridization
FLC	free light chain
G-CSF	granulocyte-colony stimulating factor
GCP	Good Clinical Practice
GM-CSF	granulocyte macrophage-colony stimulating factor
GR	glucocorticoid receptor
GSH	glutathione
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
hr	hour
HR-QoL	health-related quality of life
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
Ig	immunoglobulin

Abbreviation or Specialist Term	Explanation
iFISH	interphase fluorescence in situ hybridization
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
IRC	Independent Review Committee
ISS	International Staging System
ITT	intent-to-treat
IV	intravenous
Karyopharm	Karyopharm Therapeutics Inc.
KPT-330	selinexor
KM	Kaplan-Meier
LDH	lactate dehydrogenase
M	visit for MM disease assessments only
mAb	monoclonal antibody
MAP	maximum a posteriori
MedDRA	Medical Dictionary for Regulatory Activities
min	minutes
MM	multiple myeloma
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGF	next generation flow
NGS	next generation sequencing
NHL	non-Hodgkin’s lymphoma
ORR	overall response rate
ORR1	overall response rate during SVdX treatment
OS	overall survival
PD	progressive disease
PDn	pharmacodynamics
PE	physical examination

Abbreviation or Specialist Term	Explanation
PET	positron emission tomography
PFS	progression-free survival
PFS1	PFS during SVdX treatment
PFS2	PFS on first post-SVd/Vd/SVdX treatment
PI	proteasome inhibitor
PK	pharmacokinetic(s)
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes
PP	per-protocol
PR	partial response
QIW	4 times per week
CCI [redacted]	[redacted]
QoL	quality of life
QW	once weekly
RBC	red blood cell
R-ISS	Revised International Staging System
RNA	ribonucleic acid
RRMM	relapsed or refractory multiple myeloma
SAE	serious adverse event
SAM	S-adenosylmethionine
SAP	statistical analysis plan
SC	subcutaneous(ly)
sCR	stringent complete response
SD	stable disease
Sd	selinexor plus low-dose dexamethasone
SdX	selinexor plus low-dose dexamethasone treatment after crossover
Sel	selinexor
SI	International System of Units
SINE	selective inhibitor of nuclear export
SOC	system organ class
SPd	selinexor plus pomalidomide plus low-dose dexamethasone
SPD	sum of the products of the maximal perpendicular diameters of measured lesions

Abbreviation or Specialist Term	Explanation
SPEP	serum protein electrophoresis
Study Manual	Manual for the study site that may include any of the following: Laboratory Manual, Pharmacy Manual, Investigator Binder, Case Report Form Guidelines, Interactive Response Technologies User Guidelines, and any other site materials that are generated for the study such as Imaging Guidelines, etc.
SUSAR	suspected unexpected serious adverse reaction
SVd	selinexor plus bortezomib plus low-dose dexamethasone
SVdX	SVd treatment after crossover
TEAE	treatment-emergent adverse event
$t_{½}$	elimination (terminal) half-life
TLS	tumor lysis syndrome
t_{max}	time to peak plasma concentration
TSP	tumor suppressor protein
TTNT	time-to-next-treatment
TTR	time to response
ULN	upper limit of normal
UPEP	urine protein electrophoresis
URL	uniform resource locator
USA	United States of America
Vd	bortezomib plus low-dose dexamethasone
VGPR	very good partial response
WBC	white blood cell
X	visit for in-clinic dosing and multiple myeloma disease assessment
XPO1	exportin 1

2. PROTOCOL SYNOPSIS

Sponsor:	**Investigational Product:**	**Study Phase:**
Karyopharm Therapeutics Inc.	Selinexor (KPT-330)	Phase 3

Title of Study:

A Phase 3 Randomized, Controlled, Open-label Study of Selinexor, Bortezomib, and Dexamethasone (SVd) versus Bortezomib and Dexamethasone (Vd) in Patients with Relapsed or Refractory Multiple Myeloma (RRMM)

Study Name:

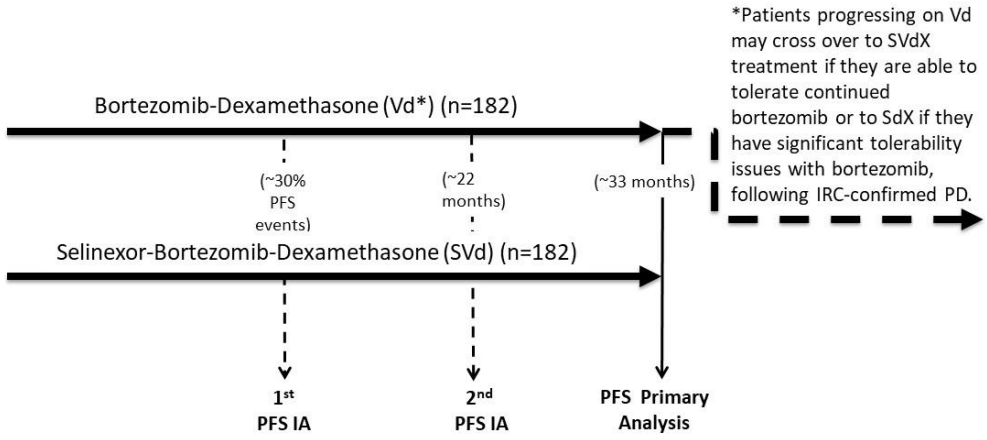
BOSTON: Bortezomib, Selinexor, and Dexamethasone in Patients with Multiple Myeloma

Protocol Number: KCP-330-023

Indication: Relapsed or refractory multiple myeloma (RRMM)

Overall Study Design: This Phase 3, 2-arm, randomized, active comparator-controlled, open-label, multicenter study will compare the efficacy and health-related quality of life (HR-QoL) and assess the safety of selinexor plus bortezomib (Velcade® or generic equivalent) plus low-dose dexamethasone (SVd) versus bortezomib plus low-dose dexamethasone (Vd) in adult patients with RRMM who have received 1 to 3 prior anti-multiple myeloma (MM) regimens. After progressive disease (PD) is confirmed by the Independent Review Committee (IRC), patients in the Vd Arm may cross over to a regimen that includes selinexor: 1) SVd treatment (SVdX) for patients who are able to tolerate continued bortezomib, or 2) selinexor and dexamethasone treatment (SdX) for patients who have significant tolerability issues with bortezomib. Patients who cross over will be referred to as SVdX patients or SdX patients, respectively.

The study overview is presented in the figure below.



- 1st IA after ~30% PFS events for possible sample size re-estimation
- 2nd IA after ~75% PFS events for futility or superiority
- PFS primary analysis (~33 months after first patient is randomized)

Abbreviations: IA = interim analysis; IRC = Independent Review Committee; ITT = intent-to-treat; PD = progressive disease; PFS = progression-free survival; SdX= selinexor plus low-dose dexamethasone treatment after crossover; SVd = selinexor plus bortezomib plus low-dose dexamethasone; SVdX = SVd treatment after crossover; Vd = bortezomib plus low-dose dexamethasone.

Study Rationale:

This study is based on preliminary supportive data from patients with relapsed MM treated with SVd in Study KCP-330-017 (STOMP; NCT02343042) demonstrating that SVd has very high levels of anti-myeloma activity, even in patients with proteasome-inhibitor (PI)-refractory disease, with relatively low adverse event (AE) rates. The majority of patients in Study KCP-330-017 (STOMP) were treated with once weekly (QW) bortezomib.

Crossover of patients on the control arm (Vd Arm) to SVdX will allow for direct assessment of selinexor's ability to restore sensitivity in PI-resistant MM.

The QW regimen of SVd, based on Study KCP-330-017 (STOMP), provides for a considerable reduction (~40%) in overall bortezomib dose versus the control arm (Vd Arm) that, in addition to the relatively low dose of selinexor, may be associated with better tolerability (eg, peripheral neuropathy) compared with second-line Vd and Vd-based combination regimens. Thus, this SVd regimen could serve a current and rapidly growing unmet medical need in patients with RRMM, providing for increased response rates and durability of response over Vd, with improved tolerability with respect to peripheral neuropathy-associated untoward effects of bortezomib.

Objectives:

Primary

Disease response will be assessed according to the International Myeloma Working Group (IMWG) response criteria based on Kumar (Kumar 2016).

- To compare progression-free survival (PFS) based on the IRC's disease outcome assessments in patients randomized to the SVd Arm versus the Vd Arm

Secondary

- To compare the overall response rate (ORR) (≥ partial response [PR]) based on the IRC's response outcome assessments in patients randomized to the SVd Arm versus the Vd Arm
- To compare the incidence of any Grade ≥2 peripheral neuropathy events in patients randomized to the SVd Arm versus patients randomized to the Vd Arm
- To compare the number of patients with response ≥ very good partial response (VGPR), ≥ complete response (CR), ≥ stringent complete response (sCR), or minimal residual disease (MRD) negative (for patients who achieve CR or sCR) in patients randomized to the SVd Arm versus the Vd Arm
- To compare overall survival (OS) in all patients randomized to the SVd Arm versus the Vd Arm
- To compare the duration of response (DOR) in patients randomized to the SVd Arm versus the Vd Arm
- To determine ORR1 (ORR during SVdX treatment only)
- To determine PFS1 (PFS during SVdX treatment only)
- To compare time-to-next-treatment (TTNT) in patients randomized to the SVd Arm versus the Vd Arm who receive post-SVd/Vd/SVdX/SdX treatment
- To compare time-to-response (TTR) in patients randomized to the SVd Arm versus the Vd Arm
- To assess the safety and tolerability of treatment with SVd versus Vd in patients with RRMM

- To compare patient-reported peripheral neuropathy as measured by the European Organization for Research and Treatment of Cancer (EORTC) Chemotherapy-induced Peripheral Neuropathy (QLQ-CIPN20) instrument in patients randomized to the SVd Arm versus the Vd Arm

Endpoints:

Primary Endpoint

- PFS, defined as time from date of randomization until the first date of PD, per IMWG response criteria, or death due to any cause, whichever occurs first. For the purposes of PFS determination, PD will be determined by the IRC.

Key Secondary Efficacy Endpoints

- ORR, defined as any response ≥PR (ie, PR, VGPR, CR, or sCR) based on the IRC's response outcome assessments, according to the IMWG response criteria. All changes in MM disease assessments will be based on baseline MM disease assessments.
- Response rates at any time prior to PD or death due to any cause, pooled and separately for the following responses: ≥VGPR, ≥CR, ≥sCR, or MRD negative (for patients who achieve CR or sCR)

Non-Key Secondary Efficacy Endpoints

- OS, defined as time to death or lost to follow-up, measured from the date of randomization until death due to any cause or until lost to follow-up, for all patients
- DOR, defined as the duration of time from first occurrence of IRC-confirmed response ≥PR until the first date of IRC-confirmed PD or death due to any cause, whichever occurs first
- ORR1 (ORR for SVdX patients only)
- PFS1 (PFS for SVdX patients only), defined as the duration of time from date of first dose of SVd treatment after crossover from the Vd Arm until the first date of PD, or death due to any cause
- TTNT, defined as duration of time from date of last dose of study treatment until the date of first dose of post-SVd/Vd/SVdX/SdX treatment
- TTR, defined as duration of time from randomization until the date of first documented response (≥PR) per IMWG response criteria
- PFS2 (PFS for patients who receive post-SVd/Vd/SVdX treatment), defined as the duration of time from the date of first dose of post-SVd/Vd/SVdX treatment until the first date of PD on post SVd/Vd/SVdX treatment, or death due to any cause

Key Secondary Safety Endpoint

- Incidence of any Grade ≥2 peripheral neuropathy events in patients randomized to the SVd Arm versus patients randomized to the Vd Arm. The incidence of any Grade ≥2 peripheral neuropathy events will be compared between the SVd Arm and the Vd Arm (using only events that occurred prior to crossover) as a secondary endpoint using the safety population.

Non-Key Secondary Safety Endpoints

- Safety and tolerability of study treatment based on AE reports, physical examination results (including vital signs), Eastern Cooperative Oncology Group (ECOG) performance status score,

12-lead electrocardiogram (ECG) results, ophthalmic examination results, and clinical laboratory results

Secondary HR-QoL Endpoint

- Patient-reported peripheral neuropathy, as measured by the EORTC QLQ-CIPN20 instrument

Study Location:

Approximately 120 global investigative sites are planned.

Number of Patients (planned):

Approximately 364 patients will be randomized. The number of patients enrolled may be adjusted based on the results of the interim analysis (IA) for sample size re-estimation (first IA).

Study Population: This study will enroll patients ≥18 years of age with RRMM who have received 1 to 3 prior anti-MM regimens and who meet all of the inclusion criteria and none of the exclusion criteria.

Randomization:

Patients (~364) will be randomized to 1 of 2 treatment arms (SVd or Vd) in a 1:1 allocation, as follows:

- SVd Arm (~182): selinexor + bortezomib (QW) + dexamethasone
- Vd Arm (~182): bortezomib (Cycles 1-8 [twice weekly], Cycles ≥9 [QW]) + dexamethasone

Randomization will be stratified based on the following stratification factors and will maintain the 1:1 allocation between treatment arms (SVd, Vd) within each of the stratification categories:

- Prior PI therapies (Yes or No)
- Number of prior anti-MM regimens (1 versus >1)
- Revised International Staging System (R-ISS) stage based on screening results (R-ISS Stage III versus R-ISS Stage I or II) (Palumbo 2015).

It is planned to randomize patients within individual countries in a 1:1 allocation to SVd:Vd.

Test Product, Dose, and Mode of Administration:

SVd Arm:

- Selinexor will be given as a fixed oral 100 mg dose (five 20 mg tablets) on Days 1, 8, 15, 22, and 29 of each 35-day cycle.
- Bortezomib will be given at a dose of 1.3 mg/m^2 SC on Days 1, 8, 15, and 22 of each 35-day cycle.
- Dexamethasone will be given as an oral 20 mg dose on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle.

Vd Arm:

- Bortezomib will be given at a dose of 1.3 mg/m^2 SC on Days 1, 4, 8, and 11 of each 21-day cycle for the first 8 cycles. For Cycles ≥9, bortezomib will be given at a dose of 1.3 mg/m^2 SC on Days 1, 8, 15, and 22 of each 35-day cycle.
- Dexamethasone will be given as an oral 20 mg dose on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle for the first 8 cycles. For Cycles ≥9, dexamethasone will be given as an oral 20 mg dose on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle.

After IRC-confirmed PD, patients in the Vd Arm may cross over to SVdX (returning to Cycle 1) if they are able to tolerate continued bortezomib or to SdX if they have significant tolerability issues with bortezomib.

Selinexor Dose Escalation

A selinexor dose escalation may be considered for patients being treated with a selinexor-containing regimen (ie, SVd Arm, SVdX treatment, or SdX treatment) who meet the following 3 criteria: 1) do not achieve at least a PR within the first 2 cycles, 2) are tolerating SVd well at dose level 0, and 3) do not have any AEs related to study treatment Grade >2 (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.03) at the time of dose escalation. For Cycles ≥3, selinexor may be increased to a fixed oral 60 mg dose twice weekly during Weeks 1 through 5. For patients who dose escalate, selinexor will be given as a fixed oral 60 mg dose on Days 1, 3, 8, 10, 15, 17, 22, 24, 29, and 31 of each 35-day cycle. Dexamethasone (20 mg) will be given on the same days as selinexor.

Duration of Treatment and Follow-up:

Study treatment (SVd, Vd, SVdX, or SdX) may continue until PD is confirmed by the IRC, Investigator or patient decision to discontinue study treatment, pregnancy, unacceptable AEs or toxicity that cannot be managed by supportive care, withdrawal of consent, death, or Sponsor decision to terminate the study. After discontinuation of SVd, Vd, SVdX, or SdX patients will be followed for survival every 3 months until the end of study (ie, when the last patient treated in the study has been followed for up to 5 years after their last dose of SVd/Vd/SVdX/SdX treatment).

Statistical Methods:

Sample Size Calculation and Statistical Power:

CCI

3. STUDY SCHEMATICS AND SCHEDULE OF ASSESSMENTS AND DOSING FOR STUDY KCP-330-023

Table 2: Schedule of Assessments for Study KCP-330-023

Activity/Assessment[a]	Section	Screening[b] D -28 to -1	C1 D1[e]	C1 Phone Call D3[f] (selinexor-containing regimens only)	MM Disease Assessment Visits (Table 13) See Table 4, Table 5, Table 6, and Table 7 ± 2 days[g]	In-clinic Dosing Visits (> C1D2) (Table 13) See Table 4, Table 5, Table 6, and Table 7 ± 2 days	EoT Visit[c] ≤14 Days Post-Last Dose	Safety Follow-up Call 30 days after last dose of treatment + 7 days	Durability of Response and Survival Follow-up Visit[d] Every 3 months until End-of-Study Section 11.7.4 ± 14 days
ICF[h]	11.1	X							
Patient History									
Inclusion/Exclusion	7.2/ 7.3	X							
Demographics	11.2.1	X							
Medical History	11.2.2	X							
Clinical Assessments									
Height	11.5.1.1	X							
Weight	11.5.1.1	X	X			X[i] (D1 of each cycle only)	X		
BSA[j]	11.5.1.1	X	X						
Vital signs[k]	11.5.1.2	X	X		X[l]	X	X		
Complete PE	11.5.1.2	X					X		
Symptom-directed PE	11.5.1.2		Perform if clinically indicated		Perform if clinically indicated				Perform if clinically indicated
ECOG	11.5.1.2	X				X (D1 of each cycle only)	X		

Activity/Assessment[a]	Section	Screening[b] D -28 to -1	C1 D1[e]	C1 Phone Call D3[f] (selinexor-containing regimens only)	MM Disease Assessment Visits (Table 13) See Table 4, Table 5, Table 6, and Table 7 ± 2 days[g]	In-clinic Dosing Visits (> C1D2) (Table 13) See Table 4, Table 5, Table 6, and Table 7 ± 2 days	EoT Visit[c] ≤14 Days Post-Last Dose	Safety Follow-up Call 30 days after last dose of treatment + 7 days	Durability of Response and Survival Follow-up Visit[d] Every 3 months until End-of-Study Section 11.7.4 ± 14 days
Ophthalmic examination	11.5.1.4	X[m]			Perform if clinically indicated		X		
12-lead ECG[n]	11.5.1.3	X[m]			Perform if clinically indicated		X		
Laboratory Assessments		May be performed more frequently if clinically indicated, or at the Investigator's discretion							
Urinalysis	11.5.2.1	X[m]					X		
CBC with differential	11.5.2.1	X[o]			X	X (C1D8 only)	X		
Complete serum chemistry	11.5.2.1	X	X		X	X (C1D8 only)	X		
Coagulation tests	11.5.2.1	X[m]					X		
Pregnancy test (if applicable)[p]	11.5.2.2	X				X (D1 of each cycle only)	X		
C-reactive protein	11.7.1	X[m]					X		
PK at Selected Investigational Sites (up to 25 patients per arm)									
Vd Arm subset: Blood draws for bortezomib PK testing	11.4					X (C2D11 only)[q]			
SVd Arm subset: Blood draws for bortezomib and selinexor PK testing	11.4					X (C2D15 only)[q]			

Activity/Assessment[a]	Section	Screening[b] D -28 to -1	C1 D1[e]	C1 Phone Call D3[f] (selinexor-containing regimens only)	MM Disease Assessment Visits (Table 13) See Table 4, Table 5, Table 6, and Table 7 ± 2 days[g]	In-clinic Dosing Visits (> C1D2) (Table 13) See Table 4, Table 5, Table 6, and Table 7 ± 2 days	EoT Visit[c] ≤14 Days Post-Last Dose	Safety Follow-up Call 30 days after last dose of treatment + 7 days	Durability of Response and Survival Follow-up Visit[d] Every 3 months until End-of-Study Section 11.7.4 ± 14 days
Multiple Myeloma Disease Assessments[g, r]									
SPEP with serum protein immunofixation[s]	11.3.1.1	X	X		X		X		X
UPEP (24-hr urine) and urine protein immunofixation[s]	11.3.1.2	X	X		X		X		X
Quantitative Ig level[s]	11.3.1.3	X	X		X		X		X
Serum FLC[s]	11.3.1.4	X	X		X		X		X
β_2-microglobulin	11.3.1.5	X					X		
LDH	11.3.1.6	X[o]					X		
Skeletal survey[t]	11.3.1.7	X			Frequency determined by the Investigator		X		Perform if clinically indicated
Clinical plasmacytoma assessment[s, u]	11.3.1.8	X	X		Perform if clinically indicated		X		Perform if clinically indicated
Bone marrow aspirate[v]	11.3.1.9	X			At the time of response for the MRD test for patients who achieve CR or sCR				Perform if clinically indicated
Bone marrow core (trephine) biopsy[w]	11.3.1.10				At the time of response to confirm CR or sCR				
HR-QoL[x]	11.6	X				X (D1 of each cycle only)	X		
Randomization	8.2	Prior to dosing of Vd/SVd							

Activity/Assessment[a]	Section	Screening[b]	C1	C1 Phone Call	MM Disease Assessment Visits (Table 13)	In-clinic Dosing Visits (> C1D2) (Table 13)	EoT Visit[c]	Safety Follow-up Call	Durability of Response and Survival Follow-up Visit[d]
		D -28 to -1	D1[e]	D3[f] (selinexor-containing regimens only)	See Table 4, Table 5, Table 6, and Table 7	See Table 4, Table 5, Table 6, and Table 7	≤14 Days Post-Last Dose	30 days after last dose of treatment	Every 3 months until End-of-Study Section 11.7.4
					± 2 days[g]	± 2 days		+ 7 days	± 14 days
Administration of study treatment	Table 8 Table 9 Table 10 Table 11		See Table 4, Table 5, Table 6, and Table 7		See Table 4, Table 5, Table 6, and Table 7	See Table 4, Table 5, Table 6, and Table 7[y]			
AE recording	12.1.2	Throughout							
SAE reporting	12.2.3	Throughout							
Concomitant medication recording	11.5.1.5		Throughout						
Nutritional consultation	11.7.2	X[m]							
Telephone contact	11.7.3			X[f]				X	
Collection of information regarding antineoplastic therapy used after EoT	11.7.1							X	X

Abbreviations: AE = adverse event; BP = blood pressure; BSA = body surface area; CBC = complete blood count; CR = complete response; CT = computed tomography; C1D1 = Cycle 1 Day 1; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; EoT = end of treatment; CCI [redacted]; FISH = fluorescence in situ hybridization; FLC = free light chain; hCG = human chorionic gonadotropin; hr = hour; ICF = informed consent form; HR-QoL = health-related quality of life; Ig = immunoglobulin; IMWG = International Myeloma Working Group; IRC = Independent Review Committee; LDH = lactate dehydrogenase; MM = multiple myeloma; MRD = minimal residual disease; PD = progressive disease; PDn = pharmacodynamics; PE = physical examination; PET = positron emission tomography; PK = pharmacokinetics; CCI [redacted]; QLQ-CIPN20 = Chemotherapy-induced Peripheral Neuropathy instrument; SAE = serious adverse event; sCR = stringent complete response; SdX = selinexor plus low-dose dexamethasone treatment after crossover; SPEP = serum protein electrophoresis; SVd = selinexor plus bortezomib plus low-dose dexamethasone; SVdX = SVd treatment after crossover; UPEP = urine protein electrophoresis; Vd = bortezomib plus low-dose dexamethasone.

[a] If study treatment is administered on a visit day, the assessments for that visit should be performed before study treatment is administered.

[b] Procedures that are performed as part of standard of care should not be repeated if they are within the Screening window and are done prior to signing the ICF.

[c] An End of Vd Treatment Visit is required for SVdX/SdX patients. See Table 3.

[d] After discontinuation of SVd, Vd, SVdX, or SdX if feasible and clinically indicated, MM evaluations should be performed every 3 months for patients who have not progressed to assess durability of response. If MM evaluations cannot be performed, at a minimum, a telephone call will be made to the patient (or the patient's family) to assess the survival status, status of the patient's MM, and overall medical condition of the patient and collect information on any antineoplastic therapies used after discontinuation of study treatment (see Section 11.7.4).

[e] SVdX/SdX patients will return to Cycle 1 for SVdX/SdX treatment. See Table 3.

[f] Only for patients being treated with selinexor-containing regimens: Telephone call with patient to evaluate supportive care medications, concomitant medications, and AEs, and to adjust supportive care as appropriate. The telephone contact with the patient must take place on C1D3.

[g] The window of ± 2 days for MM disease assessments that fall on in-clinic dosing visits may be extended to ± 7 days for MM disease assessments that fall on a day when dosing in the clinic is not required (eg, C10D29).

[h] ICF must be signed before any study-specific procedures are performed.

[i] If the patient's weight fluctuates substantially from baseline (ie, >20%) during treatment, BSA should be recalculated.

[j] BSA will be calculated on C1D1 to determine the volume of bortezomib to be administered and to ensure that no patient receives a dose of selinexor >70 mg/m^2.

[k] BP and pulse rate should be measured after the patient has been in a supine or sitting position for 5 minutes. BP should be assessed on the same arm throughout the study. Vital signs do not need to be repeated if they are performed as part of the physical examination.

[l] If the visit for MM disease assessments occurs on the same day as the in-clinic dosing visit, vital signs should only be performed once.

[m] The following assessments may be performed between Day -28 and prior to administration of study treatment on C1D1: ophthalmic examination, 12-lead ECG, urinalysis, coagulation tests, C-reactive protein, and nutritional consultation.

[n] Patients must rest for at least 5 minutes prior to the ECG recording.

[o] CBC with differential and LDH may be performed between Day -7 and administration of study treatment on C1D1.

[p] 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 ≥2 while on treatment (a negative pregnancy test must be documented prior to administration of study drug) and at the EoT Visit (serum hCG). Pregnancy testing may also be performed as clinically indicated during the study.

[q] Perform blood draws for PK analysis at the time points in Table 18. PK sampling for bortezomib will be performed for up to 25 patients in the Vd Arm and PK sampling for bortezomib and selinexor will be performed for up to 25 patients in the SVd Arm at selected investigational sites that can accommodate patients for up to 4 hours. Details for PK sample collection and processing can be found in the *Study Manual*.

[r] Patients randomized to the SVd Arm who have IRC-confirmed PD while they are on SVd treatment will discontinue SVd treatment, proceed to the EoT Visit, and be followed for survival. Patients randomized to the Vd Arm who have IRC-confirmed PD while they are on Vd treatment and meet the criteria in Section 6.2 may cross over to a regimen that includes selinexor (Table 3): 1) SVd treatment (SVdX) for patients who are able to tolerate continued bortezomib, or 2) selinexor and dexamethasone treatment (SdX) for patients who have significant tolerability issues with bortezomib. Patients who do not elect to cross over to SVdX or SdX from the Vd Arm will discontinue treatment, proceed to the EoT Visit, and be followed for survival.

[s] Samples for MM disease assessments on C1D1 must be collected either on Day -1 or predose on C1D1 for baseline values. For patients who achieve CR or sCR, confirmatory samples for SPEP with serum protein immunofixation, quantitative Ig, and serum FLC must be collected in duplicate at the time of response and the duplicate samples must be provided to the central laboratory. A confirmatory 24-hour urine sample must also be collected and an aliquot will be provided to the central laboratory for UPEP with urine protein immunofixation. Refer to the *Study Manual* for details.

[t] A baseline skeletal survey is to be performed within 45 days prior to C1D1. Skeletal imaging does not need to be repeated in Cycle 1. Skeletal survey results will be read by the local laboratory.

[u] If plasmacytomas are detected at baseline by physical examination/palpation within 28 days prior to C1D1, they should be counted and measured per IMWG guidelines and recorded, and then reassessed during the symptom-directed physical examination on C1D1 (unless the baseline assessment was performed within 7 days prior to C1D1) and on visits for MM evaluations (if clinically indicated), at the EoT Visit, and every 3 months (if clinically indicated) during Survival Follow-up until PD or initiation of new antineoplastic therapy.

[v] A portion of the bone marrow aspirate collected at Screening for all patients will be provided to the central laboratory for karyotyping and FISH analysis and for separation of CD138- and CD138+ cell fractions for subsequent transcriptomic, genomic, and/or proteomic analyses. A portion of the bone marrow aspirate collected at the time of response for patients in either arm who achieve CR or sCR will be provided to the central laboratory for the MRD test. Refer to the *Study Manual* for details. Bone marrow aspiration may also be performed, as clinically indicated, to assess progression.

[w] A tissue block collected at the time of response for patients in either arm who achieve CR or sCR will be provided to the central laboratory. Refer to the *Study Manual* for details. A bone marrow core (trephine) biopsy may also be performed, as clinically indicated, to assess progression.

[x] Patient will complete all of the HR-QoL instruments (ie, CCI EORTC-QLQ-CIPN20, CCI) on these visits before any study-related procedures (including discussions with medical personnel and other study-related evaluations).

[y] If selinexor and dexamethasone dosing falls on the day of a visit for MM disease assessments, dosing should be performed in the clinic.

Patients who cross over to SVdX or SdX after IRC-confirmed PD, will have an End of Vd Treatment Visit and a C1D1 Visit for SVdX or SdX Treatment (Table 3). At the discretion of the Investigator, these visits may be combined. After the C1D1 Visit for SVdX or SdX Treatment, SVdX and SdX patients will follow the schedule in Table 2.

SVdX (Table 6) and SdX (Table 7) patients will undergo MM evaluations every 5 weeks.

Table 3: Unique Visits Required for Crossover to SVdX or SdX: Separate OR Combined Visits

Separate Visits		Combined Visits[a]
End of Vd Treatment Visit (within 14 days after IRC PD confirmation[b])	**Separate C1D1 Visit for SVdX or SdX Treatment**[c] (>5 days and ≤14 days after IRC PD confirmation)[b]	**End of Vd Treatment Visit and C1D1 Visit for SVdX or SdX Treatment Combined** (>5 days and ≤14 days after IRC PD confirmation)[b]
Informed consent for SVdX or SdX treatment[d]		Informed consent for SVdX or SdX treatment[d]
All assessments for EoT Visit in Table 2, including MM disease assessments (SPEP, UPEP, serum protein and urine protein immunofixation, quantitative Ig, serum FLC, and clinical plasmacytoma assessment)	MM disease assessments (SPEP, UPEP, serum protein and urine protein immunofixation, quantitative Ig, serum FLC, and clinical plasmacytoma assessment)	All assessments for EoT Visit in Table 2, including MM disease assessments (SPEP, UPEP, serum protein and urine protein immunofixation, quantitative Ig, serum FLC, and clinical plasmacytoma assessment)
	BSA Vital signs Nutritional consultation	BSA Vital signs Nutritional consultation

Abbreviations: BSA = body surface area; EoT = end of treatment; FLC = free light chain; Ig = immunoglobulin; IRC = Independent Review Committee; MM = multiple myeloma; PD = progressive disease; SdX = selinexor plus low-dose dexamethasone treatment after crossover; SPEP = serum protein electrophoresis; SVd = selinexor plus bortezomib plus low-dose dexamethasone; SVdX = SVd treatment after crossover; UPEP = urine protein electrophoresis; Vd = bortezomib plus lowdose- dexamethasone.

[a] The End of Vd Treatment Visit and the C1D1 Visit for SVdX or SdX treatment may be combined at the discretion of the Investigator.

[b] PD confirmation date is the date the IRC informs the site that PD has been confirmed.

[c] If the C1D1 Visit for SVdX/SdX Treatment is a separate visit from the End of Vd Treatment Visit, the clinical and laboratory assessments performed at the End of Vd Treatment Visit do not need to be repeated and the symptom-directed physical examination listed for C1D1 in Table 2 does not need to be performed. However, MM disease assessments and the nutritional consultation must be performed on C1D1.

[d] Informed consent for SVdX/SdX treatment must be signed before conducting any study-specific procedures for SVdX/SdX.

3.1. Schedules of Visits for In-clinic Dosing and MM Evaluations

Table 4: SVd Arm: Schedule of Visits for In-clinic Dosing and MM Evaluations

	Week 1							Week 2							Week 3							Week 4							Week 5						
	Day																																		
Cycles	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
1	X							C							C							X													
2	C							X							C							C							M*						
3	C							C							X							C													
4	X							C							C							X													
5	C							X							C							C							M*						
6	C							C							X							C													
7	X							C							C							X													
≥8	C							X							C							C													

Abbreviations: X = Visit for in-clinic dosing and MM disease assessment; C = Visit for in-clinic dosing only; M = Visit for MM disease assessments only; MM = multiple myeloma; SVd = selinexor plus bortezomib plus low-dose dexamethasone.
*Note: On C2D29 and C5D29, selinexor and dexamethasone dosing should be performed in the clinic during MM disease assessment visits.

Table 5: Vd Arm: Schedule of Visits for In-clinic Dosing and MM Evaluations

	Week 1							Week 2							Week 3							Week 4							Week 5						
	Day																																		
Cycles	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
1	X			C				C			C																								
2	X			C				C			C																								
3	X			C				C			C																								
4	X			C				C			C																								
5	X			C				C			C																								
6	X			C				C			C																								
7	X			C				C			C																								
8	X			C				C			C																								
9	X							C							C							X													
10	C							X							C							C							M						
≥11	C							C							X							C													

Abbreviations: X = Visit for in-clinic dosing and MM disease assessment; C = Visit for in-clinic dosing only; M = Visit for MM disease assessments only; MM = multiple myeloma; Vd = bortezomib plus low-dose dexamethasone.

Table 6: SVdX Treatment: Schedule of Visits for In-clinic Dosing and MM Evaluations

	Week 1							Week 2							Week 3							Week 4							Week 5						
	Day																																		
Cycles	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
≥1	X							C							C							C													

Abbreviations: X = Visit for in-clinic dosing and MM disease assessment; C = Visit for in-clinic dosing only; MM = multiple myeloma; SVd = selinexor plus bortezomib plus low-dose dexamethasone; SVdX = SVd treatment after crossover.
Note: SVdX will follow the dose schedule for SVd (Table 8).

Table 7: SdX Treatment: Schedule of Visits for In-clinic Dosing and MM Evaluations

	Week 1							Week 2							Week 3							Week 4							Week 5						
	Day																																		
Cycles	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
≥1	X																																		

Abbreviations: X = Visit for in-clinic dosing and MM disease assessment; MM = multiple myeloma; SdX = selinexor plus low-dose dexamethasone treatment after crossover.
Note: SdX will follow the dose schedule in Table 11.

3.2. Dose Schedules

Table 8: SVd Arm/SVdX Treatment Dose Schedule; 5-Week (35-Day) Cycle

SVd/ SVdX[a]	Week 1							Week 2							Week 3							Week 4							Week 5						
	Day																																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
SVd/SVdX Dose Schedule																																			
Sel[b]	X							X							X							X							X						
Bort[c]	X							X							X							X	Rest period												
Dex[d]	X	X						X	X						X	X						X	X						X	X					
Selinexor Dose Escalation for Cycles ≥3: Only Considered for Patients in the SVd Arm or on SVdX Treatment Who Meet the Following 3 Criteria: 1) Do Not Achieve At Least a PR Within the First 2 Cycles, 2) Are Tolerating SVd or SVdX Well at Dose Level 0, and 3) Do Not Have Any AEs Related to Study Treatment Grade >2 (NCI CTCAE v. 4.03) at the Time of Dose Escalation																																			
Sel[e]	X		X					X		X					X		X					X		X					X		X				
Bort[c]	X							X							X							X	Rest period												
Dex[d]	X		X					X		X					X		X					X		X					X		X				

Abbreviations: AE = adverse event; BIW = twice weekly; Bort = bortezomib; BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events; D = day; Dex = dexamethasone; eCRF = electronic case report form; MM = multiple myeloma; NCI = National Cancer Institute; PR = partial response: QW = once weekly; SC = subcutaneous; Sel = selinexor; SVd = selinexor plus bortezomib plus low-dose dexamethasone.

[a] If the patient's weight fluctuates substantially from baseline (ie, >20%) during treatment, BSA should be recalculated.

[b] Selinexor will be given as a fixed oral 100 mg dose QW. In no case may the selinexor dose exceed 70 mg/m^2 per dose for any patient.

[c] Bortezomib will be given at a dose of 1.3 mg/m^2 SC QW during Weeks 1 through 4, followed by a 13-day rest period.

[d] Dexamethasone will be given as an oral 20 mg dose BIW (ie, a total of 40 mg weekly). For patients who develop partial intolerance to glucocorticoids during the study (as determined by the Investigator), a dose reduction to a minimum dose of 10 to 12 mg dexamethasone BIW (ie, a total of 20 to 24 mg weekly) is permitted after a clear documentation of intolerance. Any dose reductions should be documented in the patient's research record and the eCRF.

[e] Selinexor may be given as a fixed oral 60 mg dose BIW during Weeks 1 through 5 of Cycles ≥3.

Table 9: Dose Schedule for Vd Arm Cycles 1 through 8; 3-Week (21-day) Cycle

	Week 1							Week 2							Week 3						
	Day																				
Vd	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Bort[a]	X			X				X			X	Rest period									
Dex[b]	X	X		X	X			X	X		X	X									

Abbreviations: BIW = twice weekly; Bort = bortezomib; Dex = dexamethasone; eCRF = electronic case report form; SC = subcutaneous; Sel = selinexor; QIW = 4 times per week; Vd = bortezomib plus low-dose dexamethasone.

[a] Bortezomib will be given at a dose of 1.3 mg/m^2 SC BIW during Weeks 1 and 2 of each cycle, followed by a 10-day rest period. If the patient's weight fluctuates substantially from baseline (ie, >20%) during treatment, BSA should be recalculated.

[b] Dexamethasone will be given as an oral 20 mg dose QIW (ie, a total of 80 mg weekly) during Weeks 1 and 2 of each cycle. For patients who develop partial intolerance to glucocorticoids during the study (as determined by the Investigator), a dose reduction to a minimum dose of 10 to 12 mg dexamethasone BIW (ie, a total of 20 to 24 mg weekly) is permitted after a clear documentation of intolerance. Any dose reductions should be documented in the patient's research record and the eCRF.

Table 10: Dose Schedule for Vd Arm Cycles ≥9; 5-Week (35-day) Cycle

	Week 1							Week 2							Week 3							Week 4							Week 5						
	Day																																		
Vd	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
Bort[a]	X							X							X							X	Rest period												
Dex[b]	X	X						X	X						X	X						X	X						X	X					

Abbreviations: BIW = twice weekly; Bort = bortezomib; D = day; Dex = dexamethasone; eCRF = electronic case report form; QW = once weekly; SC = subcutaneous; Sel = selinexor; Vd = bortezomib plus low-dose dexamethasone.

[a] Bortezomib will be given at a dose of 1.3 mg/m^2 SC QW during Weeks 1 through 4, followed by a 13-day rest period. If the patient's weight fluctuates substantially from baseline (ie, >20%) during treatment, BSA should be recalculated.

[b] Dexamethasone will be given as an oral 20 mg dose BIW (ie, a total of 40 mg weekly) during Weeks 1 through 5. For patients who develop partial intolerance to glucocorticoids during the study (as determined by the Investigator), a dose reduction to a minimum dose of 10 to 12 mg dexamethasone BIW (ie, a total of 20 to 24 mg weekly) is permitted after a clear documentation of intolerance. Any dose reductions should be documented in the patient's research record and the eCRF.

Table 11: Dose Schedule for SdX Patients; 5-Week (35-Day) Cycle

	Week 1							Week 2							Week 3							Week 4							Week 5						
	Day																																		
Sd[a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
Sd Dose Schedule																																			
Sel[b]	X							X							X							X							X						
Dex[c]	X	X						X	X						X	X						X	X						X	X					
Selinexor Dose Escalation for Cycles ≥3: Only Considered for Patients Who Meet the Following 3 Criteria: 1) Do Not Achieve At Least a PR Within the First 2 Cycles on Sd, and 2) Are Tolerating Sd Well at Dose Level 0, and 3) Do Not Have Any AEs Related to Study Treatment Grade >2 (NCI CTCAE v. 4.03) at the Time of Dose Escalation																																			
Sel[d]	X		X					X		X					X		X					X		X					X		X				
Dex[c]	X		X					X		X					X		X					X		X					X		X				

Abbreviations: AE = adverse event; BIW = twice weekly; BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events; D = day; Dex = dexamethasone; eCRF = electronic case report form; MM = multiple myeloma; NCI = National Cancer Institute; PR = partial response: QW = once weekly; SC = subcutaneous; Sel = selinexor; Sd = selinexor plus low-dose dexamethasone.

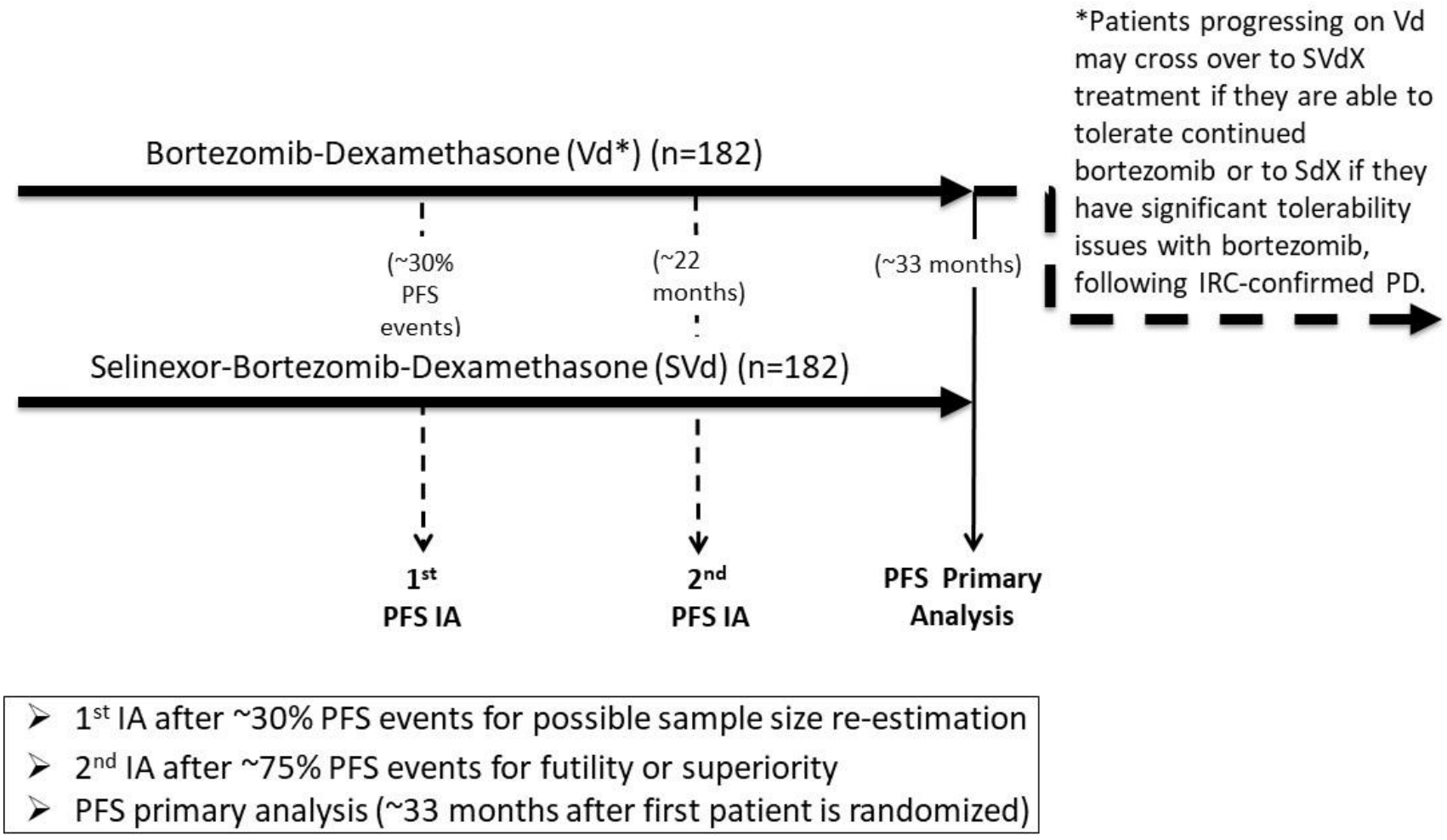
[a] If the patient's weight fluctuates substantially from baseline (ie, >20%) during treatment, BSA should be recalculated.

[b] Selinexor will be given as a fixed oral 100 mg dose QW. In no case may the selinexor dose exceed 70 mg/m^2 per dose for any patient.

[c] Dexamethasone will be given as an oral 20 mg dose BIW (ie, a total of 40 mg weekly). For patients who develop partial intolerance to glucocorticoids during the study (as determined by the Investigator), a dose reduction to a minimum dose of 10 to 12 mg dexamethasone BIW (ie, a total of 20 to 24 mg weekly) is permitted after a clear documentation of intolerance. Any dose reductions should be documented in the patient's research record and the eCRF.

[d] Selinexor may be given as a fixed oral 60 mg dose BIW during Weeks 1 through 5 of Cycles ≥3.

Figure 1: Study KCP-330-023 Overview



Abbreviations: IA = interim analysis; IRC = Independent Review Committee; ITT = intent-to-treat; PD = progressive disease; PFS = progression-free survival; SdX = selinexor plus low-dose dexamethasone treatment after crossover; SVd = selinexor plus bortezomib plus low-dose dexamethasone; SVdX = SVd treatment after crossover; Vd = bortezomib plus low-dose dexamethasone.

4. INTRODUCTION

4.1. Multiple Myeloma

4.1.1. Disease Background

Multiple myeloma (MM) is the second most common hematological malignancy (after non-Hodgkin's lymphoma [NHL]), representing 1% of all cancers and 2% of all cancer deaths. With over 30,000 new cases and approximately 12,700 deaths from MM anticipated in 2018 in the United States of America (USA) (ACS 2018) and about twice as many in Europe, there is an unmet medical need for therapies in patients with relapsed or refractory multiple myeloma (RRMM) that has progressed on available agents.

4.1.2. MM Treatment

The treatment of MM has improved over the last 20 years and overall survival (OS) has increased considerably with the approval of non-chemotherapeutic agents including immunomodulatory drugs, such as thalidomide, lenalidomide, and pomalidomide, and the proteasome inhibitors (PIs) bortezomib, carfilzomib, and oral ixazomib (which was approved more recently). These agents have served as "backbone" therapies for patients with MM, are often used in combination (eg, lenalidomide with bortezomib), and are typically combined with "low-dose" dexamethasone (ie, ≤40 mg/week). Additional drug classes, including histone deacetylase inhibitors such as panabinostat, along with anti-CD38 (daratumumab) and anti-CS1 (elotuzumab) monoclonal antibodies (mAbs), have recently been approved and are all contributing to prolonged survival in MM. Despite this progress, essentially all patients will develop refractory MM and succumb to the disease.

The prognosis remains poor for patients with RRMM who have already received at least 1 prior anti-MM regimen. For these patients, the median progression-free survival (PFS) is 6.2 to 9.4 months with bortezomib (Richardson 2007, Dimopoulos 2016) and median OS is approximately 29.8 months (Richardson 2007).

Second-line combination therapies have a significant burden of toxicity with extended sequelae, representing significant unmet medical need. Peripheral neuropathy, in particular, has an extended long-term burden for patients.

4.2. Selinexor

A summary of the relevant background information for selinexor, including the mechanism of action, nonclinical and clinical studies, and potential risks is presented below. Please refer to the Selinexor Investigator's Brochure (IB) for more detailed information.

4.2.1. Selinexor Mechanism of Action

Selinexor is an oral, first-in-class, slowly reversible, potent selective inhibitor of nuclear export (SINE) compound that specifically blocks exportin 1 (XPO1). Selinexor binds covalently to cysteine 528 in the cargo binding pocket of XPO1 and shuts down its nuclear export activity (Neggers 2016, Neggers 2015, Hing 2016). This results in marked nuclear accumulation of TSPs

and their functional reactivation as well as abrupt reduction of eIF4E transcriptionally-dependent proto oncogene proteins. Activation of TSPs and downregulation of proto-oncogenes block the cell division cycle and induce apoptosis across a range of solid and hematologic tumor cells in vitro and in vivo, while sparing normal cells.

4.2.2. Selinexor Pharmacodynamics and Dosing Frequency

Nonclinical studies have demonstrated that SINE compound binding to XPO1 results in a rapid and sustained loss of XPO1 protein expression and nuclear export function with a reciprocal induction of XPO1 mRNA (Ranganathan 2012, Tai 2014, Zhang 2013). Furthermore, by determining the time course and dose dependence of XPO1 target binding by selinexor, it has been demonstrated that selinexor target occupancy correlates with inhibition of XPO1 function (Crochiere 2016). These studies demonstrated that significant XPO1 inhibition is sustained for up to 72 hours following a single dose of selinexor, with the level of XPO1 mRNA induction and the duration of XPO1 inhibition varying with the dose. This long pharmacodynamic (PDn) half-life for selinexor supports once weekly (QW) to twice weekly (BIW) dosing for doses in the range of 60 to 100 mg.

The PDn of the selinexor effect on XPO1 mRNA in leukocytes from adult and pediatric patients in solid tumor and hematological cancer studies has been evaluated. XPO1 mRNA expression is significantly induced by 2 hours post-selinexor dose and reaches a plateau of approximately 4- to 6-fold, which is sustained for at least 48 hours (Abdul Razak 2016, Alexander 2016). Predose XPO1 mRNA expression is maintained at a level comparable to the fold induction achieved following the first dose, indicating that the maximal XPO1 inhibition in leukocytes following the first dose is maintained throughout the dosing schedule.

4.2.3. Selinexor Pharmacokinetics

The pharmacokinetics (PK) of selinexor has been investigated in 3 completed Phase 1 studies in patients with hematological and solid tumor malignancies as described. Overall, PK parameters were similar in all 3 Phase 1 studies including patients with advanced hematologic malignancies (Study KCP-330-001), advanced solid tumors (Study KCP-330-002), and advanced soft tissue or bone sarcomas (Study KCP-330-003).

Selinexor is orally bioavailable in patients with hematological and solid tumor malignancies. The absorption is moderately rapid with a median time to peak plasma concentration (t_{max}) of 2 to 4 hours. In dose escalation studies in patients with hematological and solid tumor malignancies (KCP-330-001 and KCP-330-002), selinexor exhibited linear PK, and dose-proportional exposure (area under the concentration versus time curve [AUC] and maximum plasma concentration [C_{max}]). At the therapeutic dose of 80 mg (~45 mg/m^2), the mean C_{max} was 680 ng/mL (1.5 µM) and $AUC_{0-\infty}$was 5386 ng•hr/mL. Moreover, the consistent t_{max} and elimination (terminal) half-life ($t_{½}$) across the range of doses evaluated (3 to 85 mg/m^2) suggest overall dose-independent absorption and clearance.

PK analyses support the use of fixed, rather than body surface area (BSA)-based, dosing for selinexor. Pooled analyses of data from Studies KCP-330-001, -002, and -003, indicated that BSA-adjusted dosing of selinexor did not reduce interpatient variability. Additionally, the impact of body weight- or BSA-normalized dosing regimens were evaluated in a population PK analysis. The population PK analysis confirmed the original observation that plasma selinexor

exposure was generally not affected by BSA within each dose category (low dose of <30 mg/m^2; mid-dose of 30 to 55 mg/m^2, and a high dose of >55 mg/m^2), with the exception of the lowest end of the low-dose category. These results suggest that there is limited value to adjusting patient dose by BSA or weight and therefore support fixed-dose administration.

4.2.4. Selinexor Metabolism/Drug-drug Interactions

Metabolism data suggest that clinically relevant inhibition of the major CYP450s by selinexor is unlikely in the clinical setting and no induction of CYP450 activity has been observed. In human plasma, the primary route of metabolism is via glucuronidation and subsequent hepatobiliary elimination. Given the route of metabolism and elimination of selinexor, the rapid onset of target inhibition, and the long PDn half-life, selinexor PDn are not expected to be impacted by co-administration of other drugs.

Selinexor is not expected to alter exposures of other drugs. Across clinical studies of selinexor in >2500 patients with advanced cancers treated with selinexor alone or in combination to date, no significant drug-drug interactions have been reported. In population PK analyses, the exposures to selinexor were not altered in the presence of any of the major human CYP modifiers, including CYP3A4 inhibitors or inducers. Patients also received comedications which are inhibitors of CYP2C9/19 (eg, fluconazole), CYP2D6 (eg, bupropion, paroxetine, terbinafine), and CYP1A2 (eg, ciprofloxacin). No overt differences in PK leading to adverse events (AEs) were observed for selinexor and no major changes in the AE profile of these (or other concomitant) drugs were reported. Selinexor does not accumulate over time, thus further minimizing its potential for drug-drug interactions.

Additional PK analysis will be conducted to evaluate the impact of coadministration of anticancer agents, including bortezomib, on the selinexor population PK model.

4.2.5. Selinexor Nonclinical Combination with Dexamethasone and Proteasome Inhibitors

In nonclinical models, the combination of SINE compounds with dexamethasone demonstrates synergistic anti-myeloma effects. This synergism emanates from at least 2 effects of the drug combination. The first is the induction of total of glucocorticoid receptor (GR) protein levels and the second is through the direct suppression of the mTOR pathway by the drug combination (Argueta 2018).

Nonclinical studies in vitro and in vivo have shown that selinexor strongly synergizes with PIs such as bortezomib (Turner 2013, Turner 2016, Tai 2014, Wu 2016) and carfilzomib (Kandarpa 2013, Rosebeck 2016) leading to inhibition of cell proliferation and induction of MM cell death. The mechanism for the synergy includes (a) nuclear IκB retention and inhibition of NF-κB transcriptional activity (Kashyap 2016, Turner 2016), (b) enhanced nuclear localization and activation of TSP levels (Turner 2013, Wu 2016) and (c) induction of autophagy (Kandarpa 2013, Rosebeck 2016). Moreover, as demonstrated by Turner (Turner 2016), in models of bortezomib resistant disease (refractory patient MM cells; rodent PI inhibitor resistant xenograft models), combining selinexor and bortezomib induced synergistic apoptotic cell death, tumor growth inhibition, and increased survival.

Importantly, bone marrow mononuclear cells isolated from patients with myeloma refractory to PIs are sensitized by selinexor to bortezomib and carfilzomib ex vivo, as shown by increased

induction of apoptosis by the combination with no increased effect on normal non-myeloma cells (Turner 2016). These findings mirror the clinical findings that combination treatment of selinexor and PIs can result in durable responses in patients with MM, including those whose disease is refractory to PIs.

4.2.6. Overall Clinical Experience with Selinexor

To date, more than 2500 patients with hematologic or solid tumors have received selinexor in clinical studies (including Karyopharm-sponsored studies and Investigator-sponsored studies) in >10 disease indications, the majority of patients were treated with selinexor as a single agent but >300 patients received selinexor in combination with a diverse array of other anticancer agents.

Single-agent Phase 1 studies with oral selinexor have been conducted in advanced hematological malignancies including MM, acute myeloid leukemia (AML), NHL, and chronic lymphocytic leukemia (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, diffuse large B-cell lymphoma, glioblastoma, gynecological malignancies, and dedifferentiated liposarcoma (Phase 2 and 3).

In Studies (KCP-330-001 and KCP-330-012) alone, 227 patients with MM have been exposed to selinexor ± dexamethasone:

- Results of the Phase 1 Study KCP-330-001 indicate that selinexor ± low-dose dexamethasone (20 mg QW) has clear anti-MM activity in heavily pretreated patients.
- In Part 2 of the ongoing pivotal Phase 2 Study KCP-330-012 (STORM), treatment with selinexor 80 mg with dexamethasone 20 mg (Sd), both orally twice per week, resulted in an ORR of 25.4% and a CBR (patients with ≥MR) of 39.3% in patients entering the study with rapidly progressive disease refractory to currently available MM therapies with known clinical benefit (ie, penta-exposed, triple class-refractory MM). Median duration of response was 4.4 months. The median OS in the patients with any response (≥MR; n=39) was significantly longer than those with a best response of PD/NE ($p<0.0001$), and was even longer in patients with a best response of SD (39.3% of patients) compared with patients who had PD/NE. Despite the highly aggressive nature of the MM in the patients, the Sd regimen was able to halt MM disease progression (SD or better) in ~80% of the patients entering the study (Study KCP-330-012 CSR).

Selinexor is also being studied in combination with PIs (ie, bortezomib and carfilzomib):

- Preliminary results of Study KCP-330-017 (STOMP; NCT02343042) in patients with relapsed and/or refractory MM have shown that adding selinexor to subcutaneous (SC) bortezomib and oral dexamethasone (SVd regimen) resulted in improved response rates (Section 4.2.6.1).
- Final results of a Phase 1 investigator-sponsored study (IST; NCT02199665) evaluating the combination of selinexor with carfilzomib and low-dose dexamethasone in patients with RRMM demonstrate encouraging activity (Jakubowiak 2016). The ORR for 19 patients with heavily pretreated MM was 63%.

4.2.6.1. Study KCP-330-017 (STOMP)

Study KCP-330-017 (STOMP) is an ongoing Phase 1b/2 study of selinexor in combination with multiple backbone therapies for the treatment of relapsed and/or refractory MM. The study is designed to independently assess the efficacy and safety of multiple regimens (with selinexor dose escalations within each arm), including selinexor and low-dose dexamethasone plus either bortezomib (SVd), pomalidomide (SPd), or lenalidomide.

As of the data cut off of 05 June 2018, 40 patients treated with SVd were evaluable for response. Best responses based on interim unaudited data are provided in Table 12.

Preliminary results include the following (Bahlis 2017):

- The high ORR rate of 83% in patients with PI-relapsed or PI-naïve MM treated with ≤3 prior therapies treated with SVd and the PFS of 17.8 months in patients with PI-relapsed or PI-naïve MM treated with SVd support this BOSTON study evaluating SVd vs. Vd.
- The ORR of 84% in patients with PI-relapsed or naïve MM treated with SVd is higher than the expected ORR ≤65% with Vd alone.
- The ORR of 43% in patients with PI-refractory MM treated with SVd supports the nonclinical findings that selinexor resensitizes and overcomes resistance to PIs (Section 4.2.5).
- An ORR of 83% in PI-relapsed or naïve patients with ≤3 prior treatments (ie, the "BOSTON" Phase 3 population).
- Responses on SVd were rapid and typically occurred within 1 cycle of treatment, often improving over time.

Table 12: KCP-330-017 Best Responses in Evaluable SVd Patients as of 05 June 2018

Category[a]	N[b]	ORR (%)	CBR (%)	sCR (%)	CR (%)	VGPR (%)	PR (%)	MR (%)	SD (%)	PD (%)
PI-Relapsed or Naïve	19	16 (84%)	18 (95%)	1 (5%)	3 (16%)	3 (16%)	9 (47%)	2 (11%)	1 (5%)	--
PI-Refractory	21	9 (43%)	14 (67%)	--	1 (5%)	4 (19%)	4 (19%)	5 (24%)	6 (29%)	1 (5%)
PI-Relapsed or Naïve, ≤3 Prior Treatments (BOSTON[c])	18	15 (83%)	16 (89%)	1 (6%)	3 (17%)	4 (22%)	7 (39%)	1 (6%)	2 (11%)	--

Abbreviations: CBR + clinical benefit rate (ORR+MR); CR + complete response; IMWG = International Myeloma Working Group; M = minor response; ORR = overall Response Rate (sCR+CR+VGPR+PR); PD = progressive disease; PR = partial response; sCR = stringent complete response; SD = stable disease; VGPR = very good partial response.

[a] Responses as of 05 June 2018 based on interim unaudited data. Responses were adjudicated according to the IMWG criteria.

[b] Two patients not evaluable for response: 1 death unrelated to myeloma and 1 withdrawal of consent before disease follow-up.

[c] BOSTON: patient population eligible for the ongoing Phase 3 Randomized BOSTON Study of SVd versus Vd.

The maximum tolerated dose (MTD) was not reached and prolonged tolerability and efficacy were observed in the SVd cohort.

The most common treatment-related AEs in the SVd Arm were nausea, anorexia, fatigue, and diarrhea, all mainly Grades 1-2, and thrombocytopenia with minimal bleeding. Peripheral neuropathy (all cases unrelated to selinexor) was limited to 6 patients (Grade 1: 4 patients, Grade 2: 2 patients) of which 5 had prior bortezomib exposure. This incidence rate is consistent with the published data cited in the literature (discussed below) for QW bortezomib dosing.

Based on the results from the dose escalation phase, the recommended Phase 2 dose (RP2D) is a 5-week cycle with selinexor 100 mg QW continuous, bortezomib 1.3 mg/m^2 SC QW for Weeks 1 through 4, and dexamethasone 20 mg on Days 1 and 2 BIW continuous. An expansion phase at the RP2D is currently ongoing with preliminary tolerability and efficacy results consistent with above findings.

Of note, the QW recommended regimen of SVd in STOMP uses 40% less bortezomib and 25% less dexamethasone compared with standard BIW (for 2 of every 3 weeks) Vd regimens, and consequently is expected to have significantly less peripheral neuropathy and other significant AEs than standard Vd, as well as to be more convenient for patients than standard Vd and the majority of Vd combinations, which require BIW clinic visits for SC (or intravenous [IV]) administration of bortezomib (Richardson 2007, Dimopoulos 2016, Palumbo 2016, Bringhen 2010).

These preliminary results appear to confirm the nonclinical data supporting the additive or synergistic effects of selinexor in combination with PIs (Section 4.2.5), with good tolerability, and support this BOSTON study of SVd versus Vd.

4.2.7. Potential Risks of Selinexor

At the time of the most recent Selinexor IB update, clinical experience with selinexor had been evaluated in 1672 patients (as of the 31 March 2018 safety data analysis).

In ongoing clinical studies, the most commonly reported TEAEs have been low-grade and reversible, including nausea, fatigue, anorexia, vomiting, and diarrhea; thrombocytopenia and anemia, which can be higher grade, have been also reported primarily in patients with hematologic malignancies.

In a previous study, 1 patient, heavily pretreated for recurrent pancreatic cancer, developed acute cerebellar syndrome following 3 doses of selinexor at 85 mg/m^2 (approximately 145 mg) BSA BIW. The patient experienced abnormal speech and loss of coordination, and was unable to walk. This patient recovered to near baseline with both speech and mobility over ~6 weeks. No other adult patients have reported similar symptoms to date.

Eight tumor lysis syndrome (TLS) cases have been reported, including 5 patients with MM, 1 patient with AML, and 2 patients with acute lymphoblastic leukemia; as of the date of this amendment), including 4 patients in company-sponsored studies, 2 patients in Investigator-sponsored studies, and 2 patients in the expanded access program (compassionate use). Further details about these patients are provided in Section 12.1.2.3.1.

4.2.7.1. Reproductive Risks for Selinexor

Macroscopic and microscopic changes in reproductive organs were noted during rat and monkey toxicology studies, most of which partially or fully 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.

It is unknown whether similar effects may occur in humans. As it is unknown whether selinexor might have reproductive toxicity in humans, patients must agree to use effective contraception (see Contraception Requirements, Section 10.8.1) during the study and for 3 months following the last dose of study treatment.

4.3. Bortezomib and Dexamethasone (Vd)

Bortezomib, a modified dipeptidyl boronic acid, is a reversible inhibitor of the mammalian proteasome, demonstrating rapid inhibition of 20S proteasome activity in peripheral blood following drug administration (Velcade® Prescribing Information). Bortezomib systemic exposure is equivalent following either SC or IV administration; plasma concentrations show multi-exponential decline with a rapid initial phase followed by a prolonged terminal phase and extensive peripheral tissue distribution. Peak PDn activity is achieved within 5 to 30 minutes postdose and declines slowly over the dosing interval with 22 to 48% inhibition of 20S activity observed at 48 hours postdose (Moreau 2012, Reece 2011). Bortezomib is cytotoxic to a variety of cancer cell types and causes a delay in tumor growth in nonclinical tumor models, including MM.

In the USA, Canada, and Europe, bortezomib (a first-in-class PI) is approved for the treatment of both newly diagnosed and relapsed MM. In RRMM, bortezomib is given with low-dose dexamethasone as a standard treatment worldwide. SC administration of bortezomib showed comparable efficacy to IV administration with lower rates of all AEs, in particular high-grade peripheral neuropathy (Richardson 2003, Richardson 2005, Moreau 2011). SC BIW bortezomib with low-dose dexamethasone (Vd) represents a standard, approved therapy for early relapsed MM despite recent approvals of new MM therapies.

The safety and efficacy profiles of Vd have been extensively documented in multiple randomized, controlled studies. Furthermore, the well-established dose and combinability of the Vd control arm have supported its use in multiple recent (NCT02136134 and NCT01568866) and ongoing (NCT01734928 and NCT02755597) pivotal myeloma studies.

Please refer to the full prescribing information for bortezomib (different local/regional trade names may be used) for the most current clinical experience and safety and reproductive risk information.

4.4. Study and Dose Rationale

4.4.1. Study Rationale

This Phase 3 study of SVd versus Vd in patients with RRMM, who have received 1 to 3 prior anti-MM regimens, is based on preliminary supportive safety and efficacy data from patients with relapsed MM treated with SVd in the Phase 1b/2 Study KCP-330-017 (STOMP)

demonstrating that SVd has very high levels of anti-myeloma activity, even in patients with PI-refractory disease, and a relatively low incidence of AEs (Section 4.2.6.1).

This SVd regimen could serve a current and rapidly growing unmet medical need in patients with RRMM, providing for increased response rates and durability of response over Vd, with improved tolerability with respect to peripheral neuropathy-associated untoward effects of bortezomib.

Crossover of patients on the control arm (Vd Arm), which is a commonly used backbone therapy for patients with RRMM throughout the world (Section 4.3), to SVdX following Independent Review Committee (IRC)-confirmed progressive disease (PD) will allow for direct assessment of selinexor's ability to restore sensitivity in PI-resistant MM (Section 4.2.5). Crossover from the Vd Arm to SdX will be allowed, following IRC-confirmed PD, as compassionate use for patients who are not able to tolerate continued treatment with bortezomib (Section 6.2).

4.4.2. Dose Rationale

The rationale for the proposed dosing regimen used in this BOSTON study is based on the totality of clinical safety, efficacy, PK, and PDn data from Company- and Investigator-sponsored studies of selinexor and is supported by nonclinical pharmacology data for selinexor and other SINE compounds. The QW regimen of oral selinexor (100 mg), SC bortezomib (1.3 mg/m^2), and oral dexamethasone (20 mg), which is the RP2D in Study KCP-330-017 (STOMP), enables sustained concomitant inhibition of nuclear export and proteasome activity while limiting treatment-emergent adverse events (TEAEs) such as fatigue, thrombocytopenia, and peripheral neuropathy. The high rate of response, good safety and tolerability profile, and reduced treatment burden on patients observed with this dose regimen in Study KCP-330-017 (STOMP) support its prospective investigation in the BOSTON study.

This dose regimen is supported by the following findings:

- Selinexor synergistically sensitized MM cells to the cytotoxic effects of PIs in vitro, in vivo and ex vivo while not affecting peripheral blood or non-myeloma bone marrow mononuclear cells (Section 4.2.5).
- Data from patients enrolled in Study KCP-330-017 (STOMP) demonstrate that the combination of QW bortezomib with selinexor and low-dose dexamethasone has very high levels of anti-myeloma activity with relatively low AE rates, even in patients with PI-refractory disease (Section 4.2.6.1).
- The use of QW bortezomib is associated with relatively low levels of peripheral neuropathy even with extended dosing and reduced treatment burden on patients with only 1 clinic visit per week (Section 4.2.6.1). Moreover, when used in combination in clinical studies, QW bortezomib shows similar activity and superior tolerability to BIW combination regimens (Section 4.4.2.1).
- As QW dosing of selinexor and bortezomib aligns the long PDn half-lives of both agents (Section 4.2.2 and Section 4.3 at their respective targets and limits effects on maturation of immune cell subsets, QW dosing is associated with low level cytopenias.

4.4.2.1. Bortezomib QW Dose Rationale

The QW dose schedule provides for a considerable reduction (~40%) in overall bortezomib dose versus the control arm (Vd Arm) that, in addition to the relatively low dose of selinexor, may be associated with better tolerability (eg, reduced peripheral neuropathy) compared with current second-line Vd and Vd-based combination regimens.

Varying the dose regimen of bortezomib from QW to BIW was explored in 3 patients in the Study KCP-330-017 (STOMP). Following DLT clearance in 4 patients at the dose level of selinexor 80 mg QW and bortezomib 1.3 mg/m^2 QW, 3 patients were treated with selinexor 80 mg QW and bortezomib 1.3 mg/m^2 BIW. All patients had MM that was refractory to a PI therapy. Responses were early and occurred within 1 month of treatment initiation. Response rates and duration on study were similar between these 2 dose groups (bortezomib QW [1 VGPR, 1 PR, 1 minimal response (MR), 1 PD] versus bortezomib BIW [2 PRs, 1 MR, 1 PD]) and also in comparison with the ORR for all SVd treated patients. However, all patients on BIW bortezomib were dose reduced to QW bortezomib following Cycle 1 due to increased fatigue or cytopenias.

Other clinical studies have also compared bortezomib combinations that utilize QW versus BIW bortezomib doses and have shown similar response rates between the 2 arms with improved tolerability in the QW dose group (Bringhen 2010, Mateos 2014, Reeder 2010).

Based on these results, the efficacy and tolerability of the SVd regimen using QW bortezomib has been demonstrated to be optimal. Furthermore, the expected response rate of Vd regimen in patients with 1-3 prior therapies is approximately 60% (Palumbo 2016). Results from the ongoing Study KCP-330-017 (STOMP) for SVd in PI-relapsed or naive MM are promising with an ORR of 84%.

5. STUDY OBJECTIVES AND ENDPOINTS

Disease response will be assessed according to the International Myeloma Working Group (IMWG) response criteria (based on Kumar 2016, Table 17).

5.1. Objectives

5.1.1. Primary Objective

- To compare PFS based on the IRC's disease outcome assessments in patients randomized to the SVd Arm versus the Vd Arm

5.1.2. Secondary Objectives

- To compare the ORR (≥ PR) based on the IRC's response outcome assessments (Section 6.4), in patients randomized to the SVd Arm versus the Vd Arm
- To compare the incidence of any Grade ≥2 peripheral neuropathy in patients randomized to the SVd Arm versus patients randomized to the Vd Arm
- To compare the number of patients with response ≥ VGPR, ≥ CR, ≥ sCR, or minimal residual disease (MRD) negative (for patients who achieve CR or sCR) in patients randomized to the SVd Arm versus the Vd Arm
- To compare OS in all patients randomized to the SVd Arm versus the Vd Arm
- To compare the DOR in patients randomized to the SVd Arm versus the Vd Arm
- To determine ORR1 (ORR during SVdX treatment only)
- To determine PFS1 (PFS during SVdX treatment only)
- To compare time-to-next-treatment (TTNT) in patients randomized to the SVd Arm versus the Vd Arm who receive post-SVd/Vd/SVdX/SdX treatment
- To compare time-to-response (TTR) in patients randomized to the SVd Arm versus the Vd Arm
- To compare PFS2 (PFS on first post-SVd/Vd/SVdX treatment) in patients randomized to the SVd Arm versus the Vd Arm who receive post-SVd/Vd/SVdX treatment
- To assess the safety and tolerability of treatment with SVd versus Vd in patients with RRMM
- To compare patient-reported peripheral neuropathy as measured by the European Organization for Research and Treatment of Cancer (EORTC) Chemotherapy-induced Peripheral Neuropathy (QLQ-CIPN20) instrument in patients randomized to the SVd Arm versus the Vd Arm

5.1.3. Exploratory Objectives

CCI [redacted]

5.1.4. Pharmacokinetic Objective

- To assess PK of bortezomib and selinexor in a subset of patients randomized to each arm (ie, the SVd Arm versus the Vd Arm). The effect of co-administration of bortezomib with selinexor on bortezomib or selinexor plasma levels will be evaluated.

5.2. Endpoints

5.2.1. Primary Endpoint

- PFS, defined as time from date of randomization until the first date of PD, per IMWG response criteria, or death due to any cause, whichever occurs first. For the purposes of PFS determination, PD will be determined by the IRC.

5.2.2. Secondary Efficacy Endpoints

5.2.2.1. Key Secondary Efficacy Endpoints

- ORR, defined as any response ≥PR (ie, PR, VGPR, CR, or sCR) based on the IRC's response outcome assessments, according to the IMWG response criteria. All changes in MM disease assessments will be based on baseline MM disease assessments.
- Response rates at any time prior to PD or death due to any cause, pooled and separately for the following responses: ≥VGPR, ≥CR, ≥sCR, or MRD negative (for patients who achieve CR or sCR)

5.2.2.2. Non-Key Secondary Efficacy Endpoints

- OS, defined as time to death or lost to follow-up, measured from the date of randomization until death due to any cause or until lost to follow-up, for all patients
- DOR, defined as the duration of time from first occurrence of IRC-confirmed response ≥PR until the first date of IRC-confirmed PD or death due to any cause, whichever occurs first
- ORR1 (ORR for SVdX patients only)

- PFS1 (PFS for SVdX patients only), defined as the duration of time from date of first dose of SVd treatment after crossover from the Vd Arm until the first date of PD, or death due to any cause
- TTNT, defined as duration of time from date of last dose of study treatment until the date of first dose of post-SVd/Vd/SVdX/SdX treatment
- TTR, defined as duration of time from randomization until the date of first documented response (≥PR) per IMWG response criteria
- PFS2 (PFS for patients who receive post-SVd/Vd/SVdX treatment), defined as the duration of time from the date of first dose of post-SVd/Vd/SVdX treatment until the first date of PD on post SVd/Vd/SVdX treatment, or death due to any cause

5.2.3. Secondary Safety Endpoints

5.2.3.1. Key Secondary Safety Endpoint

- Incidence of any Grade ≥2 peripheral neuropathy events in patients randomized to the SVd Arm versus patients randomized to the Vd Arm. The incidence of any Grade ≥2 peripheral neuropathy events will be compared between the SVd Arm and the Vd Arm (using only events that occurred prior to crossover) as a secondary endpoint using the safety population.

5.2.3.2. Non-Key Secondary Safety Endpoints

- Safety and tolerability of study treatment based on AE reports, physical examination results (including vital signs), Eastern Cooperative Oncology Group (ECOG) performance status score, 12-lead electrocardiogram (ECG) results, ophthalmic examination results, and clinical laboratory results

5.2.4. Secondary HR-QoL Endpoint

- Patient-reported peripheral neuropathy, as measured by the EORTC-QLQ-CIPN20 instrument

5.2.5. Exploratory Endpoints

CCI

5.2.6. PK Endpoints

- Bortezomib and selinexor PK parameters may include, but are not limited to, estimations of maximum plasma concentration (C_{max}), area under the concentration versus time curve (AUC), and time to peak plasma concentration (t_{max}).

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design and Plan

This Phase 3, 2-arm, randomized, active comparator-controlled, open-label, multicenter study will compare the efficacy and HR-QoL and assess the safety of selinexor plus bortezomib (Velcade® or generic equivalent) plus low-dose dexamethasone (SVd) versus bortezomib plus low-dose dexamethasone (Vd) in adult patients with RRMM who have received 1 to 3 prior anti-MM regimens.

The study overview is presented in Figure 1.

Approximately 364 patients will be randomized from up to 120 global investigative sites.

Patients will be randomized to 1 of 2 treatment arms (SVd or Vd) in a 1:1 allocation, as follows:

- SVd Arm (~182 patients): selinexor + bortezomib (QW) + dexamethasone
- Vd Arm (~182 patients): bortezomib (BIW)+ dexamethasone

Randomization (Section 8.2) will be stratified based on:

- Prior PI therapies (Yes or No)
- Number of prior anti-MM regimens (1 versus >1)
- R-ISS stage at study entry, based on screening results (R-ISS Stage III versus R-ISS Stage I or II) (Palumbo 2015). If data for chromosomal abnormalities (CA) and serum lactate dehydrogenase (LDH) required for R-ISS staging are not available, patients will be assigned to the R-ISS category corresponding to their ISS stage.

It is planned to randomize patients within individual countries in a 1:1 allocation to SVd:Vd.

The number of patients enrolled may be adjusted based on the results of the interim analysis (IA) for sample size re-estimation (first IA).

Patients in the Vd Arm who have PD that is confirmed by the IRC will be allowed to cross over to a regimen that includes selinexor: 1) SVd treatment (SVdX) for patients who are able to tolerate continued bortezomib, or 2) SdX for patients who have significant tolerability issues with bortezomib, following the process described in Section 6.2. Patients who cross over will be referred to as SVdX patients or SdX patients, respectively (Section 6.2).

The Schedule of Assessments is provided in Table 2. Patients will have in-clinic visits for dosing of study treatment during MM evaluations (Table 13) and telephone contacts (Section 11.7.3).

Table 13: In-clinic Dosing and MM Evaluations

Assessments[a]	MM Evaluation Visits	In-clinic Dosing Visits
Weight, ECOG, HR-QoL, and pregnancy test (serum hCG or urine)		Day 1 of each cycle[b]
CBC with differential and serum chemistry	X	C1D8 only
SPEP, UPEP, quantitative Ig level, serum FLC, clinical plasmacytoma assessment (if clinically indicated)	X	
Skeletal survey	Frequency determined by the Investigator	
Bone marrow aspirate and biopsy	At the time of response to confirm CR or sCR	
Administration of study treatment		X
Symptom-directed physical examinations	If clinically indicated	
Vital signs, AE and concomitant medication recording, and SAE reporting	X	X
Ophthalmic exam and 12-lead ECG	If clinically indicated	

Abbreviations: AE = adverse event; BSA = body surface area; CXDX = Cycle X Day X; CBC = complete blood count; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FLC = free light chain; hCG = human chorionic gonadotropin; HR-QoL = health-related quality of life; Ig = immunoglobulin; SAE = serious adverse event; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

[a] See Table 2 for details on assessments/schedule.

[b] BSA should be recalculated if weight fluctuates substantially from baseline (ie, >20%) during treatment.

The Schedule of Visits for In-clinic Dosing and MM Evaluations is provided in Table 4 for the SVd Arm, in Table 5 for the Vd Arm, in Table 6 for SVdX patients, and in Table 7 for SdX patients. Patients randomized to the SVd and Vd Arms will undergo MM evaluations every 3 weeks from baseline MM evaluations on C1D1 (regardless of dose interruptions) through the first day of Week 37 (ie, 12 MM evaluations after C1D1) to identify patients who progress quickly, then every 5 weeks for the remainder of the study regardless of cycle length. This will result in comparable PFS data from both arms. SVdX/SdX patients will undergo MM evaluations every 5 weeks.

Dose schedules are provided in Section 3.2.

Dose modifications for selinexor to manage tolerability will be allowed (see Section 10.4). Information on dose modifications for the other agents is provided in Section 10.4.3 (bortezomib) and Section 10.4.4 (dexamethasone).

Study treatment (SVd, Vd, SVdX, or SdX) may continue until PD is confirmed by the IRC, Investigator or patient decision to discontinue study treatment, pregnancy, unacceptable AEs or toxicity that cannot be managed by supportive care, withdrawal of consent, death, or Sponsor decision to terminate the study.

If PD is suspected but the IRC does not confirm PD, patients will either remain on study treatment until PD is confirmed by the IRC or discontinue study treatment, complete the End of Treatment (EoT) Visit, and be followed for survival. An exception is allowed for patients in the Vd Arm who terminate bortezomib treatment prior to IRC-confirmed PD if the termination is

due to significant toxicities such as peripheral neuropathy and all treatment measures addressing these toxicities are exhausted and documented prior to bortezomib termination. Early termination of bortezomib should be discussed and approved by the Sponsor Medical Monitor in order to allow crossover to SdX after progression is confirmed by the IRC.

After IRC-confirmed PD:

- Patients in the SVd Arm will complete the EoT Visit and be followed for survival.
- Patients in the Vd Arm may:
  - cross over (Section 6.2) to SVdX (returning to Cycle 1) after completing the End of Vd Treatment Visit if they are able to tolerate continued bortezomib treatment,
  - cross over (Section 6.2) to SdX (returning to Cycle 1) after completing the End of Vd Treatment Visit if they are unable to tolerate continued bortezomib treatment, or
  - discontinue study treatment, complete the EoT Visit, and be followed for survival.
- SVdX patients will discontinue study treatment, complete the EoT Visit, and be followed for survival.
- SdX patients will discontinue study treatment, complete the EoT Visit, and be followed for survival.

6.2. Crossover

Crossover from the Vd Arm to a treatment that includes selinexor (ie, SVdX or SdX) will be allowed at the point of IRC-confirmed objective disease progression per the IMWG criteria for patients in the Vd Arm.

The following process will be used in order to prevent premature crossover:

1. Investigators will assess PD according to the IMWG criteria including repeat testing if PD is based on serum and/or urine M-protein, quantitative immunoglobulins for IgA/IgD, or serum free light chain (FLC). PD may also be based on new or enlarging plasmacytoma(s) or bone lesion(s) or on other symptoms and signs of clinical progression that meet the IMWG criteria.
2. All cases of PD must be confirmed by the IRC prior to crossover.
3. Crossover will not be permitted based purely on Investigator-assessed progression that does not meet any IMWG criteria for PD and cannot be verified by IRC (eg, deteriorating performance status).
4. Crossover will not be permitted if dosing of bortezomib is terminated before PD is confirmed by the IRC, unless termination of bortezomib is due to significant toxicities such as peripheral neuropathy, and all treatment measures addressing these toxicities are exhausted and documented prior to bortezomib termination. Early termination of bortezomib should be discussed and approved by the Sponsor Medical Monitor in order to allow crossover to SdX after progression is confirmed by the IRC.

5. Investigator-assessed presumptive PD events that are not confirmed by the IRC will have their PFS censored at the time of treatment discontinuation.

Patients in the Vd Arm who are able to tolerate continued bortezomib treatment will be allowed to cross over to SVdX treatment.

Patients in the Vd Arm who have significant tolerability issues with bortezomib (ie, are unable to tolerate any continued bortezomib treatment, eg, due to Grade >2 peripheral neuropathy or Grade ≥2 peripheral neuropathy with pain) will be allowed to cross over to SdX treatment.

Patients who do not elect to cross over to SVdX or SdX from the Vd Arm will discontinue treatment, proceed to the EoT Visit, and be followed for survival.

6.3. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be set up for the study to review safety data for this study. The DSMB is made up of a group of individuals with pertinent expertise that reviews, on a predetermined schedule, safety data from this clinical study. It is the DSMB's responsibility to weigh risks and benefits throughout the study's duration. The DSMB will provide oversight and safety monitoring of the study in compliance with applicable regulations, legislation and associated guidance materials for the nature of the study.

As appropriate, the DSMB will provide recommendations to the Sponsor regarding continuation, modification, or discontinuation of the study based on its assessment of the reviewed safety data. This DSMB will be composed of 4 voting members (3 oncologists and an independent statistician) who will review safety data from the study. The DSMB membership, functioning, and procedures are described in the DSMB charter.

6.4. Independent Review Committee

An IRC will be formed to review MM disease assessment data for this study, to independently assess disease response and time of PD. PD based on site generated MM disease assessment data must be confirmed by the IRC prior to discontinuing treatment from either arm (unless medically contraindicated). PD as a result of plasmacytoma(s) or bone lesion(s) will be reviewed by the IRC and results will be compared with baseline assessments. IRC confirmation of PD is required for all patients and, for those patients in the Vd Arm, confirmation is required prior to initiation of SVdX/SdX treatment in the crossover (Section 6.2). The IRC will review data (generated by the local and central laboratory) that will be used for the final analysis of the primary endpoint. The IRC's assessments of PFS 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 MM disease assessments) are described in the IRC charter.

7. STUDY POPULATION SELECTION

7.1. Study Population

This study will enroll patients ≥18 years of age with RRMM who have received 1 to 3 prior anti-MM regimens and who meet all of the inclusion criteria and none of the exclusion criteria. Inclusion/exclusion criteria will be assessed during Screening.

7.2. Inclusion Criteria

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

1. Histologically confirmed MM with measurable disease per IMWG guidelines as defined by at least 1 of the following:
   a. Serum M-protein ≥0.5 g/dL (>5 g/L) by serum protein electrophoresis (SPEP) or for immunoglobulin (Ig) A myeloma, by quantitative serum IgA levels; or
   b. Urinary M-protein excretion at least 200 mg/24 hours; or
   c. Serum FLC ≥100 mg/L, provided that the serum FLC ratio is abnormal (normal FLC ratio: 0.26 to 1.65).
2. Had at least 1 prior anti-MM regimen and no more than 3 prior anti-MM regimens. Induction therapy followed by stem cell transplant and consolidation/maintenance therapy will be considered as 1 anti-MM regimen.
3. Documented evidence of progressive MM (based on the Investigator's determination according to the IMWG response criteria) on or after their most recent regimen.
4. Prior treatment with bortezomib or other PI is allowed, provided all of the following criteria are met:
   – Best response achieved with prior bortezomib at any time was ≥ PR and with the last PI therapy (alone or in combination) was ≥ PR, AND
   – Participant did not discontinue bortezomib due to Grade ≥3 related toxicity, AND
   – Must have had at least a 6-month PI-treatment-free interval prior to C1D1 of study treatment.
5. Must have an ECOG Status score of 0, 1, or 2.
6. Written informed consent in accordance with federal, local, and institutional guidelines.
7. Age ≥18 years.
8. Resolution of any clinically significant non-hematological toxicities (if any) from previous treatments to Grade ≤1 by C1D1. Patients with chronic, stable Grade 2 non-hematological toxicities may be included following approval from the Medical Monitor.
9. Adequate hepatic function within 28 days prior to C1D1:
   a. Total bilirubin <1.5 × upper limit of normal (ULN) (except patients with Gilbert's syndrome who must have a total bilirubin of <3 × ULN), and

b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) normal to <2 × ULN.

10. Adequate renal function within 28 days prior to C1D1 (estimated creatinine clearance [CrCl] of ≥20 mL/min, calculated using the formula of Cockroft and Gault):

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

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

11. Adequate hematopoietic function within 7 days prior to C1D1: total white blood cell (WBC) count ≥1500/mm^3, absolute neutrophil count ≥1000/mm^3, hemoglobin ≥8.5 g/dL and platelet count ≥75,000/mm^3 (patients for whom < 50% of bone marrow nucleated cells are plasma cells) or ≥50,000/mm^3 (patients for whom ≥50% of bone marrow nucleated cells are plasma cells).

a. Patients receiving hematopoietic growth factor support, including erythropoietin, darbepoetin, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), and platelet stimulators (eg, eltrombopag, romiplostim, or interleukin-11) must have a 2-week interval between growth factor support and the Screening assessments, but they may receive growth factor support during the study.

b. Patients must have:

– At least a 2-week interval from the last red blood cell (RBC) transfusion prior to the Screening hemoglobin assessment, and

– At least a 1-week interval from the last platelet transfusion prior to the Screening platelet assessment.

However, patients may receive RBC and/or platelet transfusions as clinically indicated per institutional guidelines during the study.

12. Female patients of childbearing potential must have a negative serum pregnancy test at Screening. Female patients of childbearing potential and fertile male patients who are sexually active with a female of childbearing potential must use highly effective methods of contraception throughout the study and for 3 months following the last dose of study treatment. Highly effective methods of contraception are listed in Section 10.8.1.

7.3. Exclusion Criteria

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

1. Prior exposure to a SINE compound, including selinexor.
2. 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 randomization. Cancer treated with curative intent for >5 years previously and without evidence of recurrence will be allowed.

3. Has any concurrent medical condition or disease (eg, uncontrolled active hypertension, uncontrolled active diabetes, active systemic infection, etc.) that is likely to interfere with study procedures.
4. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within 1 week prior to C1D1. Patients on prophylactic antibiotics or with a controlled infection within 1 week prior to C1D1 are acceptable.
5. Active plasma cell leukemia.
6. Documented systemic light chain amyloidosis.
7. MM involving the central nervous system.
8. Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome.
9. Spinal cord compression.
10. Greater than Grade 2 peripheral neuropathy or Grade ≥2 peripheral neuropathy with pain at baseline, regardless of whether or not the patient is currently receiving medication.
11. Known intolerance, hypersensitivity, or contraindication to glucocorticoids.
12. Radiation, chemotherapy, or immunotherapy or any other anticancer therapy (including investigational therapies) ≤2 weeks prior to C1D1. Localized radiation to a single site at least 1 week before C1D1 is permitted. Glucocorticoids within 2 weeks of C1D1 are permitted. Patients on long-term glucocorticoids during Screening do not require a washout period but must be able to tolerate the specified dexamethasone dose in this study.
13. Prior autologous stem cell transplantation <1 month or allogeneic stem cell transplantation <4 months prior to C1D1.
14. Active graft versus host disease (after allogeneic stem cell transplantation) at C1D1.
15. Pregnant or breastfeeding females.
16. BSA <1.4 m^2 at baseline, calculated by the Dubois (Dubois 1916) or Mosteller (Mosteller 1987) method.
17. Life expectancy of <4 months.
18. Major surgery within 4 weeks prior to C1D1.
19. Active, unstable cardiovascular function:
    a. Symptomatic ischemia, or
    b. Uncontrolled clinically significant conduction abnormalities (eg, patients with ventricular tachycardia on anti-arrhythmics are excluded; patients with first-degree atrioventricular block or asymptomatic left anterior fascicular block/right bundle branch block will not be excluded), or
    c. Congestive heart failure of New York Heart Association Class ≥3 or known left ventricular ejection fraction <40%, or
    d. Myocardial infarction within 3 months prior to C1D1.

20. Known active human immunodeficiency virus (HIV) infection or HIV seropositivity.
21. Known active hepatitis A, B, or C infection; or known to be positive for hepatitis C virus ribonucleic acid (RNA) or hepatitis B virus surface antigen.
22. Any active gastrointestinal dysfunction interfering with the patient's ability to swallow tablets, or any active gastrointestinal dysfunction that could interfere with absorption of study treatment.
23. Any active, serious psychiatric, medical, or other conditions/situations that, in the opinion of the Investigator, could interfere with treatment, compliance, or the ability to give informed consent.
24. Contraindication to any of the required concomitant drugs or supportive treatments.
25. Patients unwilling or unable to comply with the protocol, including providing 24-hour urine samples for urine protein electrophoresis at the required time points.

8. REGISTRATION AND RANDOMIZATION

8.1. Screening and Registration

The Screening period will start once a patient has provided written informed consent to participate in the study and ends on the day of study entry (C1D1).

Patient enrollment information will be provided by the site to Karyopharm for evaluation and approval. Upon confirmation of key eligibility criteria, Karyopharm will approve enrollment of the patient. After approval by Karyopharm, the patient may be randomized. See Section 8.2 for randomization procedures.

8.1.1. Study Patient Number

Each patient will be assigned a unique patient 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 by their assigned number, date of birth, and sex. The Investigator must maintain a patient master log.

8.1.2. Rescreening

Rescreening is permitted in this study. If a patient fails any of the inclusion or exclusion criteria, a patient may be rescreened after a suitable period of time (the exact length is dependent upon the reason for the screen failure) per the documented agreement of Karyopharm and the Investigator. Any patient who is rescreened must be reconsented and will retain the same patient number. A patient may only fail screening once.

8.1.3. Screen Failures

A Screen Failure is defined as any patient who signs the informed consent form (ICF) but who is not randomized into the study. The reason for not randomizing the patient will be entered in the electronic case report form (eCRF). The demographic information, informed consent, and inclusion/exclusion pages must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experiences a serious adverse event (SAE) during the Screening period.

8.1.4. Replacement of Patients

Patients who withdraw from the study without completing at least 1 cycle due to reasons that are unrelated to study treatment and/or disease state may be replaced.

8.2. Randomization to Study Treatment

An Interactive Response Technology system will be used to perform treatment randomization. Patients will be randomized to a treatment arm in a block of randomization codes that have been assigned to the patient's country and stratum.

Randomization will be performed prior to dosing.

Randomization will be stratified based on the following stratification factors and will maintain the 1:1 allocation between treatment arms (SVd, Vd) within each of the stratification categories:

- Prior PI therapies (Yes or No)
- Number of prior anti-MM regimens (1 versus >1)
- R-ISS stage based on screening results (R-ISS Stage III versus R-ISS Stage I or II) (Palumbo 2015) (Table 14). If data for CA and serum LDH required for R-ISS staging are not available, patients will be assigned to the R-ISS category corresponding to their ISS stage.

It is planned to randomize patients within individual countries in a 1:1 allocation to SVd:Vd.

Table 14: Revised International Staging System for Multiple Myeloma

Prognostic Factor	Criteria
ISS Stage	
Stage I	β_2-microglobulin < 3.5 mg/L, serum albumin ≥3.5 g/dL
Stage II	Not ISS Stage I or III
Stage III	β_2-microglobulin ≥5.5 mg/L
CA by iFISH	
High Risk	Presence of del(17p), and/or translocation t(4;14), and/or translocation t(14;16)
Standard Risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
R-ISS Stage	
I	ISS Stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS Stage I or III
III	ISS Stage III and either high-risk CA by iFISH or high LDH

Abbreviations: CA = chromosomal abnormalities; iFISH = interphase fluorescent in situ hybridization; ISS = International Staging System; LDH = lactate dehydrogenase; R-ISS = Revised International Staging System.

Source: (Palumbo 2015).

8.3. Blinding Procedures

Not applicable, this is an open-label study.

9. DISCONTINUATION CRITERIA

9.1. Early Termination 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. If this occurs, the Sponsor will notify ethics committees (eg, Institutional Review Boards [IRBs]), Investigators, and regulatory authorities.

The Sponsor will ensure that any patients receiving study treatment at the time of early termination of the study will be given the opportunity to continue study treatment under a separate treatment protocol (eg, maintenance or extension protocol). The patients will be followed for safety and antitumor responses by the clinical site Investigators as defined in the new treatment protocol.

9.2. Discontinuation of Study Treatment and/or Withdrawal of Patients from the Study

The Investigator may remove a patient from study treatment after consultation with the Sponsor for any of the following reasons:

- Unacceptable AEs or toxicity that cannot be managed by supportive care (this must be linked in the study database to the AE or toxicity event to support discontinuation)
- Any medically appropriate reason or significant protocol violation, in the opinion of the Investigator

The Investigator must remove a patient from study treatment for any of the following reasons:

- IRC-confirmed PD. Patients in the Vd Arm who have IRC-confirmed PD and are able to tolerate continued bortezomib treatment may cross over to SVdX and continue treatment until the they have IRC-confirmed PD during SVdX treatment if they meet the criteria in Section 6.2. Patients in the Vd Arm who have IRC-confirmed PD and who have significant tolerability issues with bortezomib may cross over to SdX treatment and continue treatment until the they have IRC-confirmed PD during SdX treatment if they meet the criteria in Section 6.2.
- Patient elects to discontinue study treatment
- Pregnancy

Patients may discontinue study treatment for any reason. Patients who choose to discontinue study treatment should be encouraged to continue in the study so that follow-up information on PD and survival status may be obtained.

Patients who do not have IRC-confirmed PD while receiving study treatment but are discontinued from study treatment for other reasons will be followed for survival.

Patients may elect to withdraw consent and decline further participation in the study at any time. Patients who withdraw consent must be withdrawn from the study.

The reason for the patient's discontinuation of study treatment/withdrawal from the study must be recorded in the eCRF. The reason for discontinuation must be clearly documented in the study

database and include supporting data (ie, discontinuation for PD must be accompanied by data points in the database to support PD; additionally, if the reason for discontinuation is physician decision, ample justification must be provided and linked to PD values, AEs, etc.).

Any patient who does not withdraw from the study but who stops attending study visits and does not respond to 3 documented contact attempts will be considered lost to follow-up.

All patients will be followed until the end of the study (Section 9.3) or until they withdraw consent, are withdrawn from the study by the Investigator, have died, or have been lost to follow-up, whichever occurs first.

9.3. End of Study Definition

End of study (Last Patient, Last Visit) will be upon completion of the Survival Follow-up period for the last patient treated in the study. Completion of follow-up for the last patient will occur when the last patient in the study has been followed for up to 5 years after their last dose of SVd/Vd/SVdX/SdX treatment, has withdrawn consent, has been withdrawn from the study by the Investigator, has died, or has been lost to follow-up, whichever occurs first.

10. STUDY TREATMENTS

10.1. Treatments Administered

10.1.1. Study Treatments

Selinexor will be provided as film-coated, immediate-release tablets for oral administration in blister packs. Selinexor tablets will contain selinexor 20 mg of the Active Pharmaceutical Ingredient (API). Refer to the *Study Manual* for selinexor storage.

Bortezomib (for SC injection) and dexamethasone (oral tablets) to be used in combination with selinexor in this study will be obtained by the investigational sites, unless otherwise specified in the contractual agreement. Bortezomib and dexamethasone should be stored as described on their respective product labels.

Study treatments must be dispensed only by a pharmacist or appropriately qualified staff. Study treatments are to be dispensed only to patients enrolled in this study.

10.2. Dose Schedules and Administration

10.2.1. Labeling

All labels will include conditions for storage, lot number, and other information required by the Food and Drug Administration (FDA), International Council for Harmonisation (ICH), and/or Annex 13, and all local regulations for investigational medications.

10.2.2. Dispensing Directions

Dispensing instructions for selinexor will be provided in the *Study Manual*.

10.2.3. Dosing Information

10.2.3.1. Dosing Sequence and Timing

In general, where possible, each study treatment (ie, selinexor, bortezomib, dexamethasone) should be given at least 1 to 2 hours apart. However, on C2D15 (the day of PK sampling for patients in the PK subset of the SVd Arm), selinexor should be dosed within 15 minutes prior to bortezomib (Section 11.4).

Dexamethasone should be administered at least 1 hour before selinexor (SVd Arm) and bortezomib.

10.2.3.2. Selinexor

For details of selinexor formulation, preparation, and administration, please refer to the *Study Manual*.

Selinexor tablets should be taken orally with at least 120 mL (4 ounces) of water at approximately the same time each day. It can be taken with or without food. Selinexor tablets should be swallowed whole (not crushed) to prevent an increased risk of dermatologic toxicity if the powder comes in contact with skin.

For doses of selinexor that are to be taken on non-clinic days, the patient will be provided with selinexor by the site pharmacy and selinexor may be self-administered by the patient on an outpatient basis.

10.2.3.3. Bortezomib

For details of bortezomib formulation, preparation, and administration, please refer to the full prescribing information for bortezomib (different local/regional trade names may be used).

Bortezomib will only be administered by qualified site personnel during clinic visits in accordance with the prescribing information for bortezomib (in the appropriate local language).

10.2.3.4. Dexamethasone

For details of dexamethasone formulation, preparation, and administration, please refer to the full prescribing information for dexamethasone as it is locally available.

For doses of dexamethasone that are to be taken on non-clinic days, the patient will be provided with dexamethasone and its schedule of administration by the site pharmacy. Dexamethasone may be self-administered by the patient on an outpatient basis.

10.2.4. Dose Schedules for Evaluation

See Section 10.4 for dose modifications.

10.2.4.1. SVd Arm

The dose schedule for the SVd Arm (5-week [35-day] cycle) is provided in Table 8.

- Selinexor will be given as a fixed oral 100 mg dose on Days 1, 8, 15, 22, and 29 of each 35-day cycle.
- Bortezomib will be given at a dose of 1.3 mg/m^2 SC on Days 1, 8, 15, and 22 of each 35-day cycle.
- Dexamethasone will be given as an oral 20 mg dose on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle.

In no case may the selinexor dose exceed 70 mg/m^2 per dose for any patient (see Section 11.5.1.1).

10.2.4.2. Vd Arm

The dose schedule for **Cycles 1 through 8 (3-week [21-day] cycle)** for the Vd Arm is provided in Table 9.

- Bortezomib will be given at a dose of 1.3 mg/m^2 SC on Days 1, 4, 8, and 11 of each 21-day cycle for the first 8 cycles.
- Dexamethasone will be given as an oral 20-mg dose on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle for the first 8 cycles.

The dose schedule for **Cycles ≥9 (5-week [35-day] cycle)** for the Vd Arm is provided in Table 10.

- Bortezomib will be given at a dose of 1.3 mg/m^2 SC on Days 1, 8, 15, and 22 of each 35-day cycle.
- Dexamethasone will be given as an oral 20 mg dose on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle.

10.2.4.3. SVdX Patients

SVdX patients will return to Cycle 1 for SVd treatment (Table 8) and undergo MM evaluations every 5 weeks. SVdX patients will follow the dose schedule for the SVd Arm (Section 10.2.4.1).

10.2.4.4. SdX Patients

SdX patients will return to Cycle 1 for Sd treatment (Table 11) and undergo MM evaluations every 5 weeks.

- Selinexor will be given as a fixed oral 100 mg dose on Days 1, 8, 15, 22, and 29 of each 35-day cycle.
- Dexamethasone will be given as an oral 20 mg dose on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle.

10.2.5. Selinexor Dose Escalation

A selinexor dose escalation may be considered for patients being treated with a selinexor-containing regimen (ie, SVd Arm, SVdX treatment, or SdX treatment) who meet the following 3 criteria: 1) do not achieve at least a PR within the first 2 cycles, 2) are tolerating SVd well at dose level 0, and 3) do not have any AEs related to study treatment Grade >2 (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v. 4.03) at the time of dose escalation. The dose schedule for Cycles ≥3 for patients who have a selinexor dose escalation is provided in Table 8.

- For Cycles ≥3, selinexor may be increased to a fixed oral 60 mg dose BIW during Weeks 1 through 5. For patients who dose escalate, selinexor will be given as a 60 mg dose on Days 1, 3, 8, 10, 15, 17, 22, 24, 29, and 31 of each 35-day cycle. Dexamethasone (20 mg) will be given on the same days as selinexor.

10.2.6. Duration of Treatment and Follow-up

Study treatment (SVd, Vd, SVdX, or SdX) may continue until PD is confirmed by the IRC, Investigator or patient decision to discontinue study treatment, pregnancy, unacceptable AEs or toxicity that cannot be managed by supportive care, withdrawal of consent, death, or Sponsor decision to terminate the study.

10.3. Supportive Care for All Patients

10.3.1. Required 5-HT3 Antagonists

In order to minimize nausea, all patients should receive 5-hydroxytryptamine (5-HT3) antagonists (8 mg or equivalent) unless contraindicated, starting on C1D1 before the first dose of

study treatment and continued 2 to 3 times daily thereafter, as needed. Alternative treatment may be provided if the patient does not tolerate 5-HT3 antagonists.

10.3.2. Recommended Supportive Care

Supportive measures for optimal medical care should be provided to all patients in both arms during participation in this study. In addition to the required prophylactic therapy with 5-HT3 antagonists (Section 10.3.1), supportive care per institutional guidelines and/or the National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines in Oncology (NCCN) should be used as clinically indicated at the discretion of the Investigator.

Supportive care guidelines for managing AEs are provided in Table 16.

10.3.3. Infection

No prophylactic antimicrobial agent is recommended for most patients initiating therapy with selinexor. Patients with a history of recurrent infections or those at high risk for specific infections may continue their prophylactic antimicrobial regimens without modification when initiating selinexor therapy.

In patients who develop fever or other signs of systemic infection, an appropriate antimicrobial should be initiated immediately. Selinexor should be suspended in any patient with a Grade 4 infection or sepsis (even in the absence of documented infection) until the patient's clinical condition is stabilized. Selinexor can then be restarted at the previous dose once the patient's clinical status has stabilized, even in the setting of continued IV (and/or oral) antimicrobial agents. Selinexor is not known to have any drug interactions with standard antimicrobials. Please also see Table 16.

10.3.4. Glucocorticoid Side Effects

The management of common glucocorticoid side effects is well documented. Aggressive use of proton-pump inhibitors, anti-hypertensives, glucose-lowering drugs, 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.

10.3.5. Overdose

As selinexor is metabolized by glutathione (GSH) conjugation, it is possible, but not demonstrated, that hepatic GSH depletion might occur in case of extreme overdose. Therefore, in patients who develop liver function test abnormalities, supportive measures such as SAM or other drugs that can replace GSH might be considered as part of the overall management plan.

10.4. Dose Modifications

All dose modifications will be captured in the eCRF.

10.4.1. Selinexor Dose Reduction Guidelines

Selinexor, a specific XPO1 inhibitor, alters a variety of tumor suppressors, cell cycle regulators, oncoproteins, and transcriptional factors. Given this complex mechanism, the relationship between dose and antitumor activity, as well as tolerability, is expected to be highly dependent on both tumoral and patient factors. Consistent with this, based on observations from the ongoing studies in patients with advanced hematological and solid tumors, selinexor shows a wide therapeutic range with antitumor activity from 12 to 120 mg. Therefore, in order to optimize the antitumor activity and tolerability, dose reductions and/or schedule modifications will be allowed as outlined below and in Table 15 and Table 16. For some AEs, dose interruption rather than reduction is recommended. See Table 16 for specific recommendations.

While drug-related major organ toxicities are not prominent, thrombocytopenia and a number of constitutional side effects can limit dosing with selinexor. Therefore, patients should also be treated with supportive care to reduce toxicities (see Section 10.3). In addition, it should be noted that the constitutional side effects often attenuate over the first 4 to 6 weeks of dosing. Finally, some patients with rapid tumor responses experience significant fatigue, nausea, malaise, and/or asthenia after 1 or more doses of selinexor. This effect has not been associated with typical markers of TLS, but if suspected, assessment of tumor response is strongly recommended in order to better inform treatment recommendations.

The NCI CTCAE v. 4.03 will be used for grading the severity of AEs; the study treatment modifications described below are applied according to this severity grading. Toxicity will be documented as described in Section 12.1.3. If more than 1 type of toxicity occurs concurrently, the most severe grade will determine the modification.

Each dose modification or treatment delay, as well as the reason, must be documented (Table 15 and Table 16).

Table 15 summarizes the starting dose for selinexor (100 mg), the allowed escalation (60 mg BIW), and the preferred dose modifications (80 to 40 mg) for AEs listed in Table 16.

Table 15: Pre-specified Dose Modifications for AEs Related to Selinexor

Selinexor Dose Level	Total Weekly Selinexor Dose	Selinexor Dose Schedule
Dose Level +1[a]	120 mg	60 mg BIW (ie, 120 mg QW not allowed)
Dose Level 0 (Starting Level)	100 mg	100 mg QW
Dose Level -1	80 mg	80 mg QW
Dose Level -2	60 mg	60 mg QW
Dose Level -3	40 mg	40 mg QW

Abbreviations: AEs = adverse events; BIW = twice weekly; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; QW = once weekly.

[a] Dose level +1 may be considered for patients who meet the following 3 criteria: 1) do not achieve at least a PR after the first 2 cycles of SVd, and 2) are tolerating SVd well at dose level 0, and 3) do not have any AEs related to study treatment Grade >2 NCI CTCAE v. 4.03 at the time of dose escalation.

Table 16: Supportive Care and Selinexor Dose Adjustment Guidelines for AEs Related to Selinexor

Toxicity and Intensity	Supportive Care and Selinexor Dose Adjustment Guidelines
Fatigue[a, b]	
Grade 1	Maintain dose. Rule out other causes. If found to be anemic and symptomatic, consider transfusing even with hemoglobin >8 g/dL (anemia Grade <3). Patients with significant fatigue after several doses of selinexor may have an antitumor response. Consider an unscheduled assessment of tumor response as part of the patient's evaluation.
Grade 2 lasting ≤7 days	As per NCCN guidelines, consider stimulants such as methylphenidate 5 mg QD in the morning only.
Grade 2 lasting >7 days or Grade ≥3	Rule out other causes. If found to be anemic and symptomatic, consider transfusions for hemoglobin >8 g/dL (Grade <3); transfusions usually indicated for Hb <8 g/dL (Grade ≥3). Interrupt selinexor dosing until resolved to Grade 1 or baseline. For first occurrence, restart selinexor at current dose. For ≥ second occurrence, reduce selinexor by 1 dose level. Patients with significant fatigue after several doses of selinexor may have an antitumor response. Consider an unscheduled assessment of tumor response as part of the patient's evaluation. As per NCCN guidelines, consider stimulants such as methylphenidate 5 mg QD in the morning only.
Anorexia or Weight loss	
Grade 1 anorexia	Maintain dose. Rule out other causes. Consider nutritional consultation and use nutritional supplements (eg, Ensure®, Boost®). For persistent symptoms, initiate appetite stimulants, such as olanzapine (2.5 to 5 mg PO every morning) or megesterol acetate (400 mg QD), as per NCCN guidelines.
Grade 1 weight loss Grade 2 anorexia	Initiate appetite stimulants, such as olanzapine (2.5 to 5 mg PO every morning) or megesterol acetate (400 mg QD), as per NCCN guidelines.
Grade 2 weight loss Grade 3 anorexia, or Grade 3 weight loss	Interrupt selinexor dosing until improved to Grade 1 or baseline and weight stabilizes. Reduce selinexor by 1 dose level. Rule out other causes. Consider nutritional consultation and use nutritional supplements (eg, Ensure®, Boost®). Initiate appetite stimulants as above.

Toxicity and Intensity	Supportive Care and Selinexor Dose Adjustment Guidelines
Nausea, Acute	
Grade 1 or 2	Maintain dose. Rule out other causes. Use standard additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonists. If persistent, use additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonist(s). Olanzapine 2.5 to 5 mg PO every morning, as per NCCN guidelines, can mitigate nausea and anorexia.
Grade 3	Rule out other causes. Use additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonist(s). Olanzapine 2.5 to 5 mg PO every morning, as per NCCN guidelines, can mitigate nausea and anorexia. Interrupt selinexor dosing until resolved to Grade ≤2 or baseline and reduce selinexor by 1 dose level. Patients with significant nausea/vomiting after several doses of selinexor may have an antitumor response. Consider an unscheduled assessment of tumor response as part of the patient's evaluation.
Hyponatremia	
Grade 1 (sodium levels < Normal to 130 mmol/L)	Maintain dose. Rule out other causes including drug (eg, 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. Provide supplemental oral and/or intravenous fluids if dehydration is present. Consider addition of salt tablets to patient's diet.
Grade 3 with sodium levels <130-120 mmol/L without symptoms	Rule out other causes including drug (eg, diuretic) effects. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose >150 mg/dL). If (corrected) sodium is Grade ≤3 and continues to be asymptomatic, then patient may continue current dosing without interruption provided that IV saline and/or salt tablets are provided and patient is followed closely. If Grade 3 is persistent or worsens or does not respond to treatment, interrupt selinexor dosing until resolved to Grade 1 or baseline and reduce selinexor by 1 dose level.
Grade 3 with sodium levels <130-120 mmol/L with symptoms or Grade 4 (<120 mmol/L)	Rule out other causes including drug (eg, diuretic) effects. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose >150 mg/dL). Interrupt selinexor dosing until resolved to Grade 1 or baseline and without symptoms. Reduce selinexor by 1 dose level.
Diarrhea	
Grade 1	Maintain dose. Rule out other causes including drug effects. Treat per institutional guidelines with anti-diarrheals, such as loperamide.
Grade 2	Rule out other causes including drug effects. Treat per institutional guidelines with anti-diarrheals. Interrupt selinexor dosing until resolved to Grade 1 or baseline. For first occurrence, restart selinexor at current dose. For ≥ second occurrence, reduce selinexor by 1 dose level.
Grade 3 or 4	Interrupt selinexor dosing until resolved to Grade 1 or baseline and patient is clinically stable. Reduce selinexor dose by 1 dose level.

Toxicity and Intensity	Supportive Care and Selinexor Dose Adjustment Guidelines
Thrombocytopenia	
Grade 1 or 2	Maintain dose. Rule out other causes including drug effects.
Grade 3 without bleeding	Rule out other causes including drug effects. For first occurrence: skip 1 dose and reduce selinexor by 1 dose level. If recurrent, unless contraindicated, initiate treatment with moderate to high doses of thrombopoietin stimulating agents such as romiplostim 5 to 10 µg/kg SC weekly (preferred) or eltrombopag 100 to 150 mg QD. In cases where there is significant disease involvement in the bone marrow or pre-existing compromised marrow function (eg, due to prior marrow-toxic therapy), or if there is thrombocytopenia Grade 2 to 4 at baseline, 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. Thrombopoietin stimulating agents are recommended.
Grade 4 without bleeding	Rule out other causes including drug effects. Interrupt selinexor until patient recovers to Grade 2 or baseline. Selinexor dosing may be reduced by 1 dose level (it is recommended to have only 1 dose modification per cycle) If recurrent, unless contraindicated, initiate treatment with moderate to high doses of thrombopoietin stimulating agents as above. In cases where there is significant disease involvement in the bone marrow or pre-existing compromised marrow function (eg, 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.
Grade ≥3 with bleeding	Interrupt selinexor dosing and check platelet counts weekly until the bleeding has stopped, patient is clinically stable, and the platelets have recovered to Grade 2 or baseline. When resuming selinexor, reduce by 1 dose level. If recurrent, unless contraindicated, initiate treatment with moderate to high doses of thrombopoietin stimulating agents as above.
Neutropenia	
Grade 3 or 4 neutropenia (afebrile) OR Febrile neutropenia	Institute colony stimulating factors and prophylactic antibiotics as clinically indicated per institutional guidelines. Interrupt selinexor and check neutrophils at least weekly until recovers to Grade 2 or baseline and without fever (if febrile) and the patient is clinically stable. Reinitiate selinexor therapy and colony stimulating factors per institutional guidelines. If recurrent, continue colony stimulating factors, interrupt selinexor until neutrophil counts improve to Grade ≤2 or baseline levels, and reduce dose of selinexor 1 dose level.
Anemia	
Treat per institutional guidelines including blood transfusions and/or erythropoietins. Consider transfusing for symptoms with hemoglobin >8 g/dL (Grade <3) or for any Grade 3 (hemoglobin <8 g/dL). If possible, maintain selinexor dose as long as patient is clinically stable, but if a dose reduction or interruption is desired, consult with the Medical Monitor.	

Toxicity and Intensity	Supportive Care and Selinexor Dose Adjustment Guidelines
Tumor lysis syndrome	
If TLS risk factors are identified, provide prophylactic IV hydration and regular monitoring of hydration (especially when increasing the dose of selinexor), renal function, urine output, and clinical laboratory measures of interest for TLS (eg, phosphorus, potassium, calcium, LDH, uric acid). Consider administration of hypouricemic agents to reduce the risk of TLS. Interrupt selinexor in patient with hyperkalemia (≥7.0 mmol/L) and/or symptoms of hyperkalemia, an increase in uric acid, or other changes in biochemical blood parameters suggestive of TLS. Start IV hydration and consider hypouricemic agent until levels return to normal. Selinexor can be reintroduced at the normal or reduced dose.	
Other selinexor-related adverse events	
Grade 1 or 2	Rule out other causes. Maintain dose. Start treatment and/or standard supportive care per institutional guidelines.
Grade 3 or 4	Rule out other causes. Interrupt selinexor until recovers to Grade 2 or baseline and reduce selinexor by 1 dose level. Isolated values of Grade ≥3 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.

Abbreviations: IV = intravenous; LDH = lactate dehydrogenase; NCCN = National Comprehensive Cancer Network; QD = once daily; PO = oral; SC = subcutaneous: TLS = tumor lysis syndrome.

[a] For all Grade ≥3 hematologic or non-hematologic AEs that are NOT selinexor related, after consultation with the Medical Monitor and at the discretion of the Investigator, selinexor dosing may be maintained.

[b] For all selinexor-related AE's, if the below prescribed dose reductions/interruptions result in a stabilization of ≥4 weeks, a re-escalation may be considered after approval from the Medical Monitor.

All dose modifications should be based on the worst preceding toxicity.

Note: When toxicities due to selinexor have returned to baseline levels or the patient has stabilized, the dose of selinexor may be re-escalated in consultation with the Medical Monitor.

Additional recommendations for supportive care to help manage selinexor-related AEs are provided in Section 10.3.2.

The possibility of overlapping toxicities with bortezomib and/or dexamethasone should be considered and it is strongly recommended that the Investigator dose reduces or interrupts 1 drug at a time (see Section 10.4.2).

10.4.1.1. Selinexor Dose Adjustment in the Setting of Infection

Patients with active uncontrolled or suspected infections should have treatment withheld until the infection has clinically resolved and/or the patient is clinically stable. When ready to resume dosing, treatment may continue at the original dose. Missed doses will not be replaced. Patients may continue on antibiotics for prolonged periods while re-initiating their treatment at the discretion of the Investigator.

10.4.1.2. Conditions Not Requiring Selinexor Dose Reduction

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

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

- Isolated values of Grade ≥3 alkaline phosphatase. Determination of liver versus bone etiology should be made, and evaluation of gamma-glutamyl transferase, 5'-nucleotidase, or other liver enzymes should be performed.

10.4.2. Dose Modifications for Overlapping Toxicities

Thrombocytopenia and neutropenia are potential overlapping toxicities for selinexor with bortezomib. If a patient experiences drug-induced thrombocytopenia and/or neutropenia while receiving the combination under investigation in this study, the Investigator should attempt to determine which drug may be responsible and treat appropriately, including dose modifications, as necessary. If, during the management of an AE for an individual patient receiving both selinexor and bortezomib, the Investigator suspects that bortezomib may be the cause of that event, the Investigator should discuss the case with the Medical Monitor. If the cause cannot be attributed to a single drug, it is strongly recommended that the Investigator dose reduces or interrupts 1 drug at a time. Please refer to Table 16 for AEs presumed to be related to selinexor.

The manufacturers of bortezomib have provided dose adjustment guidelines for managing Grade 3 to 4 thrombocytopenia and neutropenia that occur during treatment with bortezomib in the prescribing information.

10.4.3. Bortezomib Dose Modifications

In the event of bortezomib-related peripheral neuropathy (Grade 1 with pain or Grade 2 [moderate symptoms; limiting instrumental activities of daily living]), during treatment with 1.3 mg/m^2 bortezomib BIW, change treatment schedule to 1.3 mg/m^2 bortezomib QW.

For all other bortezomib-related events, the bortezomib dose may be adjusted during treatment according to the guidelines in the prescribing information for bortezomib (different local/regional trade names may be used).

10.4.4. Dexamethasone Dose Modifications

The dose of dexamethasone should preferably remain constant throughout the study.

However, for patients with partial intolerance to dexamethasone, a dose reduction to a minimum dose of 10 to 12 mg dexamethasone BIW (ie, a total minimum dose of 20 to 24 mg weekly) is permitted after a clear documentation of intolerance. Any dose reductions should be documented in the patient's research record and the eCRF.

10.5. Missed or Vomited Doses

10.5.1. Missed Doses of Study Treatments (Selinexor, Bortezomib, and Dexamethasone)

Missed doses of study treatments should be managed as follows:

For doses missed for protocol- or study-related reasons (eg, due to recommendation of the Investigator, such as due to an AE):

- **Missed dose of bortezomib for patients in the Vd Arm Only:** If a bortezomib dose was missed, the schedule of that week should be altered to accommodate 2 doses in that week with at least 72 hours between 2 consecutive doses of bortezomib.

- **Missed dose of any study treatment for all patients:** If a dose of any study treatment must be missed, the next dose will be taken as per schedule. All missed and delayed doses should be documented.

For doses missed for reasons not related to the protocol/study (eg, a required medical procedure or an unanticipated personal emergency):

- If a patient missed a full 1- or 2-week period of study treatment dosing for events that are not related to the protocol or the study the days missed will be replaced. For example, if a patient missed C2D7 to C2D14, then the patient will start the next dosing on C2D7 following the break. Similarly, if a patient misses C3D1 to C3D15, then the patient will start the next dosing on C3D1.

The schedule of MM evaluations will be maintained regardless of drug holidays or drug interruptions (Section 11.3.1).

10.5.2. Vomited Doses of Selinexor

If a dose of selinexor is vomited within 1 hour of ingestion, it will be replaced. If vomiting occurs more than 1 hour after dosing, it will be considered a complete dose.

10.6. Sponsor-supplied Study Treatment Accountability

The Investigator or designee must maintain an accurate record of receipt of shipment and dispensing of Sponsor-supplied study treatment in a drug accountability log. Accountability for Sponsor-supplied study treatment will be documented throughout the study and reconciled. Patients will be asked to return all unused Sponsor-supplied study treatment and packaging on a regular basis, at the end of the study or at the time of discontinuation of selinexor. All unused Sponsor-supplied study treatment must be destroyed with accompanied documentation.

10.7. Compliance

The Investigator or other study staff will either directly administer or supervise study treatment given in the clinic and instruct the patient on study treatment self-administration, as appropriate. Patients will be asked to bring their Sponsor-supplied study treatment containers with them at each visit, and compliance with Sponsor-supplied protocol-defined study treatment intake at home will be checked by tablet count.

Compliance to oral Sponsor-supplied study treatment taken at home will be assessed by the Investigator and/or study personnel at each visit and recorded in source documents after discussion with the patient and after performing Sponsor-supplied study treatment accountability.

The Investigator will account for the number of Sponsor-supplied tablets dispensed against those returned by the patient. Any deviations and missed doses will be recorded in the eCRF and drug accountability logs along with the reasons for subsequent verification.

10.8. Contraception Requirements and Concomitant Medications

10.8.1. 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 and fertile male patients must agree to use highly effective contraception listed below (ie, results in a low failure rate when used consistently and correctly) during the dosing period and for a period of at least 3 months after the end of treatment.

Highly effective methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomized partner
- sexual abstinence

Please see Section 4.2.7.1 for additional safety information related to pregnancy.

10.8.2. Non-study-related Concomitant Medication and Treatment

Concomitant medications include any prescription or over-the-counter preparation, including vitamins, dietary supplements, over-the-counter medications, and oral herbal preparations taken during the study. 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.

10.8.2.1. Permitted Concomitant Medication

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

10.8.2.2. Use of Blood Products

During treatment, patients may receive RBC or platelet transfusions, if clinically indicated, per institutional guidelines. Patients who require repeated transfusion support should be discussed with the Sponsor.

Appropriate anti-coagulation is allowed during the study (eg, low molecular weight heparin, direct factor Xa inhibitors, etc.). Warfarin is allowed during the study provided patients are monitored for INR twice a week during the first 2 cycles of study treatment, then weekly to biweekly thereafter.

Patients may receive supportive care with erythropoietin, darbepoetin, G-CSF or GM-CSF, pegylated growth factors, and platelet stimulatory factors, in accordance with clinical practice or institutional guidelines throughout the study.

The use of blood products, transfusions, etc. will be documented in the eCRF.

10.8.2.3. Radiation Treatment

If clinically indicated, palliative radiation therapy to non-target lesions is permitted but study treatment should be held for ≥1 day before the start of palliative radiation therapy and ≥1 day following each dose of palliative radiation therapy. Study treatment shall not be discontinued solely due to palliative radiation.

10.8.3. Restrictions for Study Treatment

10.8.3.1. Restrictions for Selinexor

Medications: There are no restrictions on the use of acetaminophen or acetaminophen-containing products in combination with selinexor, EXCEPT on days of selinexor dosing, when acetaminophen use must not exceed a total daily dose of 1 g.

Patients should not take GSH-, S-adenosylmethionine (SAM)-, or N-acetylcysteine-containing products during their participation in this study as these products may enhance the metabolism of selinexor. However, they are permitted if the patient has elevated liver function tests.

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

10.8.3.2. Restrictions for Bortezomib and Dexamethasone

Refer to the full prescribing information for bortezomib (different local/regional trade names may be used) for the most current information for restrictions.

10.8.4. Prohibited Medications

Concurrent therapy with any approved or investigative anticancer therapeutic outside of those included in this study is not allowed. Use of any immunosuppressive agents during the study must be confirmed by the Sponsor. Refer to the full prescribing information for bortezomib (different local/regional trade names may be used) for the most current information on prohibited concurrent medications.

11. ASSESSMENTS

Procedures that are performed as part of standard of care should not be repeated if they are within the Screening window and are done prior to signing the ICF.

11.1. Informed Consent

Assessments may not be performed until the patient provides written informed consent (see Section 14.6).

SVdX/SdX patients will be required to sign a separate ICF for treatment with SVd/Sd.

11.2. Demographic and Baseline Characteristics Assessments

11.2.1. Demographics

Patient demographics (including date of birth, sex, race, ethnicity, and age at the time of consent) will be collected.

11.2.2. Medical History

A complete medical history will be obtained from each patient. Medical history will include baseline symptoms as well as a detailed history of prior procedures for the patient's MM and other prior cancer therapies (ie, chemotherapy, hormonal therapy, immunotherapy, biotherapy, radiotherapy, and surgery), including start and end dates, best response, PD during or after therapy, as well as discontinuations due to intolerability or toxicity. Smoking history will be recorded. A detailed history of disease-specific diagnostic and prognostic testing and test results (such as phenotypic and cytogenetic profiles) will also be collected. Evaluate the risk of TLS based on a clinical evaluation of comorbidity (such as presence of renal impairment or cardiac insufficiency).

Data from standard-of-care procedures will be part of the patient's medical history and may be used for study purposes.

11.3. Efficacy Assessments

Efficacy evaluations will be performed as described below. Refer to Table 2, Table 4, Table 5, Table 6, and Table 7 for the timing of all efficacy assessments.

11.3.1. Multiple Myeloma Disease Assessments

Patient response will be assessed by the procedures described in the following subsections and graded according to the IMWG response criteria summarized in Table 17 (Kumar 2016). 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. However, all MM disease assessments outlined below are required to be performed at the study visits specified in Table 2, Table 4, Table 5, Table 6, and Table 7 and the Investigator should make all attempts to collect all MM disease assessments at each time point as outlined in this protocol.

Patients randomized to the SVd and Vd Arms will undergo MM evaluations every 3 weeks from baseline MM evaluations on C1D1 (regardless of drug holidays or drug interruptions) through the first day of Week 37 (ie, 12 MM evaluations after C1D1) to identify patients who progress quickly, then every 5 weeks for the remainder of the study regardless of cycle length (see Table 4 and Table 5). This will result in comparable PFS data from both arms. SVdX patients (Table 6) and SdX patients (Table 7) will undergo MM evaluations every 5 weeks. If additional MM disease assessments (ie, SPEP, urine protein electrophoresis [UPEP], serum FLC, quantitative Ig, serum/urine protein immunofixation, and clinical plasmacytoma assessment) are performed at unscheduled times, those results must be documented in the eCRF as unscheduled visits.

Samples on C1D1 must be collected either on Day -1 or predose on C1D1 for baseline values.

All MM disease assessments should be performed regardless of the diagnosis that is being followed (ie, 24-hour urine collection for UPEP must be performed at each time point outlined in the protocol even if the patient is being followed by SPEP).

Two consecutive assessments are needed to confirm response (Table 17). For patients who achieve CR or sCR, confirmatory samples for SPEP with serum protein immunofixation, quantitative Ig, and serum FLC must be collected in duplicate at the time of response and the duplicate samples must be provided to the central laboratory. A confirmatory 24-hour urine sample must also be collected, and an aliquot will be provided to the central laboratory for UPEP with urine protein immunofixation. Refer to the *Study Manual* for details.

For the purposes of Risk-Based Monitoring activities, sites may be requested/required to provide de-identified laboratory results (MM disease assessments) via the electronic data capture system. Further instructions will be provided in the *Study Manual*.

Table 17: International Myeloma Working Group Response Criteria, Myeloma (Kumar, 2016)

IMWG Response Criteria[a, b, c]	
Response Subcategory	**Response Criteria**
Complete response (CR)	Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow aspirates
Stringent complete response (sCR)	CR as defined above plus normal FLC ratio[d] and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells[e]
Very good partial response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine Mprotein- level <100 mg per 24 hr
Partial response (PR)	≥50% reduction of serum M-protein plus reduction in 24-hr urinary M-protein by ≥90% or to <200 mg/24 hr.

IMWG Response Criteria[a, b, c]	
Response Subcategory	**Response Criteria**
	If the serum and urine M-protein are not measurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein and serum FLC assay are not measurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30%. In addition to the above criteria, if present at baseline, a ≥50% reduction in the size (SPD) of soft tissue plasmacytomas is also required.[f]
Minimal response (MR)	≥25% but <49% reduction of serum M-protein and reduction in 24-hr urine M-protein by 50–89%. In addition to the above criteria, if present at baseline, a ≥50% reduction in the size (SPD) of soft tissue plasmacytomas is also required.[f]
Stable disease (SD)	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for CR, VGPR, PR, MR, or PD.
Progressive disease (PD)[g, h]	Any 1 or more of the following criteria: Increase of 25% from lowest confirmed response value in 1 or more of the following criteria: Serum M-protein with absolute increase of ≥0.5 g/dL; Serum M-protein increase ≥1 g/dL if the lowest M-component was ≥5 g/dL; Urine M-protein (absolute increase must be ≥200 mg/24 hr); In patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); 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 ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in SPD[f] of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis;

IMWG Response Criteria[a, b, c]	
Response Subcategory	**Response Criteria**
	≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease
Clinical relapse	Clinical relapse requires 1 or more of the following criteria: 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 time-to-progression or PFS but is listed as something that can be reported optionally or for use in clinical practice; Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD[f] of the measurable lesion; Hypercalcaemia (>11 mg/dL); Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein
Relapse from CR (to be used only if the endpoint is diseasefree- survival)	Any 1 or more of the following criteria: Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcaemia see above)
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 cells 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 ≥5% clonal plasma cells in the bone marrow;

IMWG Response Criteria[a, b, c]	
Response Subcategory	**Response Criteria**
	Appearance of any other sign of progression (ie, 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; VGPR = very good partial response.

Source: Kumar, 2016 (Kumar 2016).

[a] 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 (eg, 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.

[b] 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 in Kumar [Kumar 2016]).

[c] Derived from international uniform response criteria for MM (Durie 2006). MR definition and clarifications derived from Rajkumar (Rajkumar 2011Rajkumar 2011Rajkumar 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 ≥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.

[d] 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).

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

[f] 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.

[g] 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.

[h] In the case where a value is felt to be a spurious result per Investigator discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

Questions regarding interpretation of the IMWG criteria (Table 17) may be addressed by consulting the, "Practical considerations for application of IMWG consensus criteria," section of the guidelines (page e340 in Kumar (Kumar 2016).

11.3.1.1. SPEP

SPEP with monoclonal protein band (M-spike) quantification and serum protein immunofixation will be performed to assess response.

11.3.1.2. UPEP

UPEP (24-hour urine) with M-spike quantification and urine protein immunofixation will be performed to assess response. 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.

11.3.1.3. Quantitative Immunoglobulin Levels

If SPEP is felt to be unreliable for routine M-protein measurement (eg, patients with IgA or IgD myeloma), then quantitative Ig levels by nephelometry is acceptable. However, this must be explicitly reported, and even though nephelometry can be used for the patient to assess response, SPEP and nephelometric values cannot be used interchangeably (Durie 2006).

11.3.1.4. Serum FLC

Serum FLC will be performed to assess response.

For patients whose disease is only measurable by serum FLC:

- CR requires negative serum and urine immunofixation plus a normal serum FLC ratio of 0.26 to 1.65 on 2 consecutive assessments. Laboratories may use their own reference ranges.
- VGPR requires >90% decrease in the difference between involved and uninvolved serum FLC levels on 2 consecutive assessments.

11.3.1.5. β2 microglobulin

β2 microglobulin will be performed for MM staging (Table 14) and will not be used to assess response.

11.3.1.6. LDH

Serum LDH will be performed for MM staging (Table 14).

11.3.1.7. Skeletal Survey

A baseline skeletal survey will be performed using X-rays and/or other clinically appropriate imaging modalities (eg, magnetic resonance imaging ([MRI], whole body computed tomography [CT], or positron emission tomography [PET]/CT) as determined by the Investigator.

The skeletal survey should include a lateral radiograph of the skull, anterioposterior and lateral views of the spine, and anterioposterior views of the pelvis, ribs, femora, and humeri.

If lytic bone lesions or plasmacytomas are observed at baseline, their number and size should be recorded in the eCRF. Bone lesions and/or plasmacytomas detected by imaging at baseline should be reassessed during the study, at a frequency determined by the Investigator, using the same imaging modality that was used at baseline to document response.

- For patients without soft tissue plasmacytomas (ie, bone lesions only), skeletal survey by X-rays or low-dose CT should be performed. Contrast is not required.
- 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.

Skeletal imaging does not need to be repeated in Cycle 1.

Skeletal survey results will be read by the local laboratory. Refer to the *Study Manual* for details.

11.3.1.8. Clinical Plasmacytoma Assessment

If plasmacytomas are detected at baseline by physical examination/palpation, they should be counted and measured per IMWG guidelines and recorded, and then reassessed as clinically indicated during the symptom-directed physical examinations.

11.3.1.9. Bone Marrow Aspirate

A bone marrow aspirate will be collected at Screening and a portion will be provided to the central laboratory for karyotyping and fluorescence in situ hybridization (FISH) analysis to confirm diagnosis and classify cytogenetic MM subtypes for R-ISS staging.

Another portion of the Screening bone marrow aspirate will be used to isolate plasma, non-tumor CD138- and tumor CD138+ cell fractions for future PDn testing (see Section 11.4.2.1). Evaluation of cytogenetic alterations will include deletion of 17p [del(17p)], a translocation of chromosome [t(4;14)], a translocation of chromosome 14 and chromosome 16 [t(14;16)], and chromosome 1q21 amplification.

A bone marrow aspirate is required at the time of response for the MRD test for patients in either arm who achieve CR or sCR, unless after consultation with the Medical Monitor the collection and/or processing of the sample is not considered to be feasible.

A portion of the bone marrow aspirate collected at the time of response will be provided to the central laboratory. Refer to the *Study Manual* for details.

MRD will be assessed by fluorescence activated cell sorting (FACS) of bone marrow aspirates. MRD results will be quantitative: MRD positive = number of malignant clones per 100,000 leukocytes >0; MRD negative = number of malignant clones per 100,000 leukocytes = 0.

Bone marrow aspiration may also be performed, as clinically indicated, to assess progression.

11.3.1.10. Bone Marrow Core (Trephine) Biopsy

At the time of response, a bone marrow core (trephine) biopsy is required to confirm CR and sCR.

A tissue block collected at the time of response for patients in either arm who achieve CR or sCR will be provided to the central laboratory. Refer to the *Study Manual* for details.

A bone marrow core (trephine) biopsy may also be performed, as clinically indicated, to assess progression.

11.4. Pharmacokinetic and Pharmacodynamic Procedures

11.4.1. Pharmacokinetic Endpoints

PK sampling will only be performed at selected investigational sites that can accommodate patients for up to 4 hours.

- PK sampling for bortezomib will be performed for up to 25 patients in the Vd Arm.
- PK sampling for bortezomib and selinexor will be performed for up to 25 patients in the SVd Arm.

Blood draws for PK analysis will be performed in accordance with Table 18. For the SVd Arm, selinexor should be dosed within 15 minutes prior to bortezomib on C2D15.

Details of PK sample collection and processing can be found in the *Study Manual*.

Plasma samples will be analyzed via validated methods for plasma bortezomib and selinexor concentrations.

PK endpoints may include, but are not limited to, estimations of C_{max}, AUC, and t_{max}.

Table 18: Collection Time Points for Bortezomib and Selinexor PK

Time Points for PK Sample Collection	**Vd Arm (bortezomib PK)**	**SVd Arm (bortezomib and selinexor PK)**
	C2D11	**C2D15**[a]
Predose (before dosing of bortezomib in the Vd Arm and before dosing of selinexor and bortezomib in the SVd Arm)	X	X
30 min (± 5 min) post-bortezomib dose	X	X
1 hr (± 10 min) post-bortezomib dose	X	X
2 hr (± 10 min) post-bortezomib dose	X	X
4 hr (± 10 min) post-bortezomib dose (if feasible)	X	X

Abbreviations: hr = hours; min = minutes; PK = pharmacokinetics; SVd = selinexor plus bortezomib plus low-dose dexamethasone; Vd = bortezomib plus low-dose dexamethasone.

[a] Selinexor should be dosed within 15 minutes prior to bortezomib on C2D15.

11.4.2. Pharmacodynamic Studies

11.4.2.1. Bone Marrow Aspirates for PDn

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's mechanism of action. 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 and chromosome 1q21 amplification. 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.

Details of PDn sample collection and processing can be found in the *Study Manual*.

11.5. Safety Assessments

Safety evaluations will be performed as described below. Refer to Table 2 for the timing of all safety assessments.

11.5.1. Clinical Safety Assessments

11.5.1.1. Weight, Height, and BSA

Height (without shoes) in centimeters and weight (indoor clothing without shoes) in kilograms will be measured. BSA will be calculated by the Dubois (Dubois 1916) or Mosteller (Mosteller 1987) method to determine the volume of bortezomib to be administered and to ensure that an individual patient's selinexor dose does not exceed 70 mg/m^2. In no case may the selinexor dose exceed 70 mg/m^2 per dose for any patient. If the patient's weight fluctuates substantially from baseline (ie, >20%) during treatment, BSA should be recalculated.

11.5.1.2. Physical Examination, Vital Signs, and ECOG Performance Status

Complete physical examinations should include general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and neurological examinations.

Symptom-directed physical examinations should include body systems as appropriate, including the presence/absence or change in size of plasmacytomas identified at Screening. These examinations will be performed according to the standards at each institution.

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

Vital signs include systolic and diastolic blood pressure (BP), pulse measurements, and body temperature (°C or °F). Vital signs should be assessed predose on the scheduled visit day, if possible. BP and pulse rate should be measured after the patient has been in a supine or sitting position for 5 minutes. BP should be assessed on the same arm throughout the study. Note: If the visit for MM disease assessments occurs on the same day as the in-clinic dosing visit, vital signs should only be performed once.

ECOG performance status assessments (Oken 1982) will be performed during the study to assess how the disease affects the daily living abilities of the patients.

11.5.1.3. Electrocardiography

A standard 12-lead ECG will be performed. Patients must rest for at least 5 minutes prior to the ECG recording. The Investigator will interpret the ECG using 1 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 Fridericia's formula (Fridericia 1920).

11.5.1.4. Ophthalmic Examination

An ophthalmic examination by an optometrist or ophthalmologist is required prior to the first dose of study treatment and should be repeated if clinically indicated during the study (eg, monitoring of pre-existing cataracts, visual disturbances).

Any patient reporting de-novo or worsening of visual symptoms should immediately be referred for further examination. All visual symptoms must be documented in the eCRF.

The ophthalmic examination is to include the following:

- Prior to dilation:
  - best corrected visual acuity
  - slit lamp examination (for cataracts or other abnormalities)
  - tonometry
- Following dilation:
  - fundoscopy
  - slit lamp examination to document lens clarity

If a cataract/lens opacity is seen during the examination, the cataract/lens opacity will be graded according to the American Optometric Association (AOA) Cataract Grading System, which is available on the AOA website (www.aoa.org).

11.5.1.5. Concomitant Medications

Concomitant medications will be documented for each patient. A detailed history of medications will be documented. At each study visit, patients will be asked whether they have taken any medication other than the study treatment. All concomitant medications including dietary supplements, over-the-counter medications, and oral herbal preparations, as well as changes in medication, will be recorded in the eCRFs.

Necessary supportive care, such as appetite stimulants, anti-emetics, anti-diarrheals, etc. is allowed (see Table 16 and Section 10.3).

11.5.1.6. Adverse Events

Information regarding AEs and SAEs will be collected. See Section 12.

11.5.2. Laboratory Safety Assessments

11.5.2.1. Clinical Laboratory Tests

Table 19 presents the clinical laboratory tests that will be performed during the study.

Table 19: Clinical Laboratory Tests

Complete Blood Count with Differential (Blood sample: whole blood + EDTA)				
Hemoglobin	Hematocrit	Mean corpuscular volume	Mean corpuscular hemoglobin	Mean corpuscular hemoglobin concentration
WBC count	WBC differential[a]	RBC count	Lymphocytes	Monocytes
Neutrophils	Eosinophils	Basophils	Platelets	
Complete Serum Chemistry (Blood sample: serum)				
Sodium	Potassium	Chloride	Bicarbonate	Urea or blood urea nitrogen[b]
Creatinine	Glucose	Calcium	Phosphate	Magnesium
ALT	AST	Alkaline Phosphatase	Total bilirubin	
Total protein	Albumin	Creatine kinase	Urate	
Coagulation				
Prothrombin time	International normalized ratio	Activated thromboplastin time		
Urinalysis[c]				
Appearance	Color	Glucose	Hemoglobin	Ketones
pH	Protein	Specific gravity		

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; EDTA = ethylenediaminetetraacetic acid; RBC = red blood cell; ULN = upper limit of normal; WBC = white blood cell.

[a] WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated.

[b] Urea (mg/dL) = Blood urea nitrogen (mg/dL) × 2.14.

[c] Microscopy will only be performed if clinically indicated.

All laboratory safety assessments will be performed and analyzed at each site by a certified local laboratory. 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 treatment) or baseline.

In addition, laboratory safety assessments will be performed and analyzed on the scheduled day, even if study treatment is being withheld. More frequent assessments may be performed if clinically indicated or at the Investigator's discretion and these should be recorded in the Unscheduled Visit eCRFs if medical decisions are made based on the results of these tests.

Any laboratory value that remains abnormal at the EoT Visit and that is considered clinically meaningful 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 graded using NCI CTCAE v 4.03.

Karyopharm must be provided with a copy of the laboratory certification and normal ranges for each parameter measured. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, Karyopharm must be provided with a copy of the certification and normal ranges for that laboratory.

11.5.2.2. 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 ≥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 ≥2 while on treatment (a negative pregnancy test must be documented prior to administration of study drug) and at the EoT Visit (serum hCG).

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

11.6. QoL Assessments

Quality of life (QoL) will be assessed using the following instruments: EORTC-QLQ-CIPN20, CCI [redacted] The EORTC QoL instruments and manuals are available on the EORTC QoL website at the following uniform resource locator (URL): http://groups.eortc.be/qol/. The EQ-5D-5L QoL instrument and manual are available on the EuroQol website at the following URL: http://www.euroqol.org.

The EORTC-QLQ-CIPN20 is a 20-item QoL instrument, which has been developed to elicit patients' experience of symptoms and functional limitations related to CIPN. The CIPN20 has 3 subscales: a sensory, motor, and autonomic subscale.

CCI [redacted]

CCI

[redacted]

11.7. Other Assessments

11.7.1. C-reactive Protein and Collection of Information on Antineoplastic Therapy

C-reactive protein will be measured and information on any antineoplastic therapies planned to be used or used after discontinuation of study treatment will be collected.

11.7.2. Nutritional Consultation

Patients must be given nutritional consultation to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with selinexor.

11.7.3. Telephone Contacts

A telephone call will be performed at the following time points:

- Selinexor-containing regimens only: On C1D3, 2 days following the first dose of selinexor on C1D1. The purpose of this telephone call is to evaluate supportive care medications, concomitant medications, and AEs, and to adjust supportive care as appropriate. The contact with the patient must take place on C1D3, 2 days following the first dose of selinexor on C1D1.
- At the Safety Follow-up. The purpose of this telephone call with the patient is to assess the overall medical condition of the patient and status of their MM, follow up on any AEs that were not resolved at the EoT Visit, and collect information regarding any antineoplastic therapies used after discontinuation of study treatment.

11.7.4. Durability of Response and Survival Follow-up Visit(s)

After discontinuation of SVd, Vd, SVdX, or SdX if feasible and clinically indicated, the following assessments should be performed at Durability of Response and Survival Follow-up Visits for patients who have not progressed to assess durability of response: SPEP with serum protein immunofixation, UPEP (24-hr) with urine protein immunofixation, quantitative Ig levels, and serum FLC (and physical examinations and imaging for bone lesions and plasmacytomas and bone marrow aspirate, if clinically indicated, per Investigator's discretion). If these assessments cannot be performed, at a minimum, a telephone call will be made to the patient (or the patient's family) to assess the survival status, status of the patient's MM, and overall medical condition of the patient and collect information on any antineoplastic therapies used after discontinuation of study treatment.

12. SAFETY DEFINITIONS, RECORDING, AND REPORTING

Note: For urgent medical issues in which the study's Medical Monitor should be contacted, please refer to the *Study Manual* for complete contact information.

12.1. Adverse Events

12.1.1. Definitions

- *Adverse event (AE)*: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.
- *Treatment-emergent adverse event (TEAE)*: Any event that was not present prior to the initiation of study treatment or any event already present that worsens in either intensity or frequency following exposure to study treatment.
- *Adverse event of special interest (AESI):* Any AE (serious or nonserious) that is of scientific and medical concern specific to the study treatment, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is appropriate.
- *Serious adverse event (SAE):* Any untoward medical occurrence that, at any dose, results in death; is life threatening (ie, an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect. (See Section 12.2.3 for additional information about SAE reporting.)

12.1.2. Recording of Adverse Events

All AEs that begin or worsen after the patient has provided informed consent will be recorded on the Adverse Events eCRF, regardless of whether dosing with study drug has commenced. For events that are considered by the Investigator to be related to the study drug, the monitoring of the AE should be continued through the end of the study, for at least 30 days following the last dose of study drug, or until resolution.

Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

The Investigator should ask the patient non-leading questions to determine if any AEs have occurred during the study, since the last study visit. Adverse events may also be recorded when they are volunteered by the patient, or through physical examination, laboratory tests, or other clinical assessments.

An AE should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity of the event, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome.

12.1.2.1. Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (ie, are considered to be clinically significant, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (eg, anemia instead of low hemoglobin).

Laboratory abnormalities that meet the criteria for an AE should be followed until they have returned to baseline levels (as measured during the Screening visit) or an adequate explanation of the abnormality is identified. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

A laboratory abnormality that does not meet the definition of an AE should not be reported as an AE. A Grade 3 or 4 event (considered to be severe per NCI CTCAE, v. 4.03) does not automatically indicate an SAE unless it meets the definition of serious as defined in Section 12.1.1 and/or as per the opinion of the Investigator. A laboratory abnormality that results in a dose being held or modified would, by definition, be an AE and must be recorded as such in the eCRFs.

12.1.2.2. Adverse Events of Special Interest

AESIs for selinexor include cataracts and acute cerebellar syndrome. All cases of cerebellar toxicity, Grade 3 or higher must be reported (see Section 12.2.3).

12.1.2.3. Other Adverse Events

12.1.2.3.1. Tumor Lysis Syndrome

As of the date of this protocol, there have been 8 reports of TLS: 4 patients in Karyopharm-sponsored studies, 2 patients in Investigator-sponsored studies, and 2 patients in the expanded access program (compassionate use). Of the 8 patients, 5 had MM reported as their underlying cancer and 3 had hematological malignancies (including 1 AML and 2 acute lymphoblastic leukemia). The event onset latency ranged from 3 to 8 days (median 4 days). The total selinexor dose prior to event onset ranged from 40 to 320 mg (median 160 mg). The outcome was reported as recovered in 4 patients and not recovered in 2 patients; the outcome was not reported in 2 patients. The Investigators assessed 7 of the events as being related to selinexor. Of the 8 cases summarized above, there were 3 cases in which the patient died as a result of a TEAE. The cause of death in each of these cases was reported as: respiratory failure secondary to advanced MM, sepsis, and respiratory failure, chemotherapy induced cardiomyopathy and acute lymphoblastic leukemia. No fatal outcomes due to TLS have been reported in any studies with selinexor, or in the ongoing EAP. Although the incidence of TLS is low (~0.3%), the causal relationship between selinexor treatment and TLS cannot be completely excluded. Early recognition of signs

and symptoms in patients at risk for TLS, including identification of abnormal clinical and laboratory values, is key and Investigators must ensure that patients being treated with selinexor maintain adequate caloric and fluid intake. Close monitoring and management of patients with hematological malignancies, including MM, for potential signs and symptoms of TLS are most relevant. See Section 10.3 for supportive care and Table 16 for selinexor dose modification guidance.

12.1.3. Adverse Event Severity

The term "severe" is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (eg, 'severe' headache). This is not the same as a "serious" AE.

The severity of the AE will be graded by the Investigator according to the NCI CTCAE Grading Scale, v. 4.03 (the NCI CTCAE files can be accessed online at the following URL: http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

If there is not a specific NCI CTCAE grading for an AE, the severity will be characterized as mild, moderate, severe, or life-threatening, according to the following definitions:

- Grade 1 (mild) events are usually transient and do not interfere with the patient's daily activities.
- Grade 2 (moderate) events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Grade 3 (severe) events interrupt the patient's usual daily activities.
- Grade 4 events are those that are considered to be life-threatening.

12.1.4. Adverse Event Causality

The Investigator will make a judgment regarding the relationship of the AE to study treatment, as defined below.

- Not related: These events will lack a temporal relationship of the event to the study treatment, making a causal relationship not reasonably possible. Exposure to other drugs, therapeutic interventions, or underlying conditions may provide a sufficient explanation for the event.
- Related: There is a temporal relationship of the event to the study treatment making 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.

12.2. Serious Adverse Events

See Section 12.1.1 for the definition of an SAE. Please note that SAEs that occur at any time between the signing of the ICF up to the first dose of study treatment, must be reported (in addition to SAEs that occur after the first dose of study treatment).

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 1 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.

12.2.1. Events that Do Not Meet the Definition of a Serious Adverse Event

Elective hospitalizations to administer, or to simplify study treatment or study procedures (ie, an overnight stay to facilitate 24-hour urine collection) or other medical procedures are not considered SAEs. A 'serious' hospitalization is defined as any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. An emergency room visit is not considered a hospitalization unless it results in an official admission as an inpatient to the hospital (eg, undesirable effects of any administered treatment) and must be documented as an SAE.

Progression of the malignancy/disease (including fatal outcomes) should NOT be reported as an SAE during the study or within the safety reporting period (see Section 12.2.3). Sudden or unexplained death should be reported as an SAE. If there is any uncertainty about a finding being due solely to progression of malignancy/disease, the finding should be reported as an AE or SAE, as appropriate.

12.2.2. Recording of Serious Adverse Events

It is the responsibility of the Investigator to record and document all SAEs occurring from the time when the ICF is signed until at least 30 days after the patient has stopped study treatment. All SAEs must be reported on the designated Sponsor's SAE Report Form in addition to being recorded in the eCRF. The original SAE report form must be retained in the Investigator's site file.

All applicable sections of the SAE Report Form must be completed in order to provide a clinically thorough report. The Investigator must assess and record the relationship of each SAE to study treatment and complete the form in English.

See ICH E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Attachment 1) for key data elements that are required for expedited reporting.

12.2.3. Reporting of Serious Adverse Events

Every SAE, regardless of the causal relationship to the study treatment, occurring after the patient has signed informed consent, until at least 30 days after the patient has stopped study treatment, must be reported to the Karyopharm Pharmacovigilance Department within 24 hours of learning of its occurrence. The investigational site personnel must use the SAE Report Form provided by Karyopharm for reporting any SAE to the Karyopharm Pharmacovigilance Department.

Upon completion, the SAE Report Form must be immediately emailed or faxed to:

Pharmacovigilance Department

Karyopharm Therapeutics Inc.

Email: pharmacovigilance@karyopharm.com

Fax: +1-617-334-7617 (USA)

+49-89-9218-5650 (Germany)

Any SAE observed after the 30-day follow-up period should only be reported to Karyopharm if the Investigator suspects that the SAE has a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported, as follow-up to the original episode, within 24 hours of the Investigator receiving the follow-up information.

An SAE should be followed until its resolution or until it is judged to be permanent. An assessment should be made at each study visit (or more frequently, if necessary) of any changes in severity of the event, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome of the event.

12.2.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Karyopharm to be related to the study treatment administered. All SUSARs 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.

In addition, Karyopharm will communicate all cases of cerebellar toxicity, Grade 3 or higher, to regulatory authorities, central ethics committees (eg, IRBs), and Investigators, in the format of an expedited Safety Report, within 7 days of awareness of the event.

If required by local regulations, the Investigator is responsible for notifying his/her IRB or local ethics committee of all SAEs.

12.3. Procedures for Handling Special Situations

12.3.1. Pregnancy and Breastfeeding

Note: Pregnancy per se is not considered to be an AE; however, it is discussed here because of the importance of reporting pregnancies that occur during studies and because a medical occurrence observed in the mother or fetus/newborn would be classified as an AE.

Female patients of childbearing potential and fertile male patients will be informed as to the potential risk of conception while participating in this study and will be advised that they must use highly effective contraception listed in Section 10.8.1 (ie, results in a low failure rate when used consistently and correctly) during the dosing period and for a period of at least 3 months after the end of treatment.

A pregnancy test will be performed on each premenopausal female patient of childbearing potential prior to the first dose of study drug, on Day 1 of Cycles ≥2 while on treatment, and again at treatment discontinuation during the End-of-Treatment visit. A negative pregnancy test must be documented prior to administration of study drug.

If a patient is confirmed pregnant during the study, study drug administration must be discontinued immediately. The Investigator must immediately notify the Sponsor's Medical Monitor of the event and record the pregnancy on the Pregnancy Form (provided by Karyopharm). The initial information regarding a pregnancy must be forwarded to Karyopharm's Pharmacovigilance by email or fax within 24 hours of first knowledge of its occurrence.

The pregnancy should be followed up to determine the outcome, including spontaneous or voluntary termination, details of the birth, and any birth defects, congenital abnormalities, or maternal and/or newborn complications.

All pregnancies occurring within 3 months after the patient's last dose of study drug must be reported to Karyopharm, regardless of whether the patient received selinexor or other study drugs, withdraws from the study, or the study is completed. Patients should be instructed to inform the Investigator regarding any pregnancies.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (described in Section 12.2.3).

A pregnancy in a female partner of a male patient must be reported to Karyopharm within 24 hours of learning of its occurrence. Pregnancies in female partners should only be followed if the male patient is being treated with a selinexor-containing regimen. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

It is not known whether selinexor passes into the breast milk. Mothers should not breastfeed while being treated with selinexor-containing regimen.

12.3.2. Overdose, Abuse, Misuse, Medication Errors, and Occupational Exposure

All incidences of overdose, abuse, misuse, medication errors, and occupational exposure are required to be reported to Karyopharm Pharmacovigilance on an SAE report form and emailed to pharmacovigilance@karyopharm.com, regardless of whether or not there is an associated AE or SAE.

12.3.2.1. Overdose

An overdose is a deliberate or accidental administration of any study treatment to a study patient, at a dose greater than that which was assigned to that patient per the study protocol. If an overdose occurs, the Investigator and Karyopharm should be notified immediately, and the patient should be observed closely for AEs. Resulting symptoms should be treated, as appropriate, and the incident of overdose and related AEs and/or treatment should be documented in the patient's medical record and in the eCRF. Information regarding the overdose is to be recorded on an SAE report form and sent to Karyopharm Pharmacovigilance regardless of whether or not an AE or SAE has occurred due to the overdose. If the overdose is associated with an SAE, the SAE report form must be submitted to Karyopharm Pharmacovigilance within

24 hours of awareness. If there is no AE or SAE, the report must be submitted within 24 hours of awareness.

As selinexor is metabolized by GSH conjugation, it is possible, but not demonstrated, that hepatic GSH depletion might occur in case of extreme overdose. Therefore, in overdose cases, if patients develop liver function test abnormalities, supportive measures such as SAM or other drugs that can replace GSH might be considered as part of the overall management plan.

12.3.2.2. Abuse, Misuse, or Medication Error

Abuse is the persistent or sporadic, intentional excessive use of the study treatment which is accompanied by harmful physical or psychological effects.

A medication error is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.

All occurrences of abuse, misuse, or medication error with any study treatment are to be recorded on an SAE report form and sent to Karyopharm Pharmacovigilance, regardless of whether or not an AE or SAE has occurred due to the abuse, misuse, or medication error. If the abuse, misuse, or medication error is associated with an SAE, the SAE report form must be submitted to Karyopharm Pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted within 24 hours of awareness.

12.3.2.3. Occupational Exposure

Occupational exposure is the exposure to a study treatment as a result of one's professional or non-professional occupation. For this protocol, please follow the instructions for preparation and administration of selinexor, bortezomib, and dexamethasone.

All occurrences of occupational exposure with any study treatment are to be recorded on an SAE report form and sent to Karyopharm Pharmacovigilance, regardless of whether or not an AE or SAE has occurred due to the occupational exposure. If the occupational exposure is associated with an SAE, the SAE report form must be submitted to Karyopharm Pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted within 24 hours of awareness.

13. STATISTICAL METHODS

A statistical analysis plan (SAP) will be finalized prior to database lock. Any changes from the statistical analyses described in this document will be described in the SAP, and any deviation from the final SAP will be described in the final report.

13.1. General Considerations

Hypothesis testing will be used for the primary efficacy endpoint and for selected secondary efficacy endpoints in order to evaluate the superiority of SVd compared with Vd. 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 2-sided 95% confidence intervals (CIs), unless stated otherwise. For continuous variables, the number of patients, mean, median, standard deviation, 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% CIs, as well as number and percentage of censored observations.

Data for the analysis of the primary endpoint will be generated by the local and central laboratory and reviewed by the IRC. The IRC's assessments of time of progression or disease response will be used as the basis for the evaluation of the primary endpoint (see Section 6.4).

13.2. Determination of Sample Size

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13.2.1. Interim Analyses

Two IAs for the primary PFS endpoint are planned.

13.2.1.1. Interim Analysis of PFS for Sample Size Re-estimation

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13.2.1.2. Interim Analysis of PFS for Futility or Superiority

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13.3. Analysis Populations

13.3.1. Intent-to-Treat Population

The intent-to-treat (ITT) population will consist of all patients who are randomized to study treatment, regardless of whether or not they receive study treatment. The ITT population will include patients who have discontinued study treatment due to toxicity or PD and patients who have died from any cause. This population will be used for primary analysis of efficacy. Patients will be analyzed in the treatment arm to which they were randomized and strata assignment at the time of randomization.

13.3.2. Per-protocol Population

The per-protocol (PP) population will consist of all ITT patients who have received at least 1 dose of study treatment and who have no major protocol violations expected to affect assessment of efficacy. Patients who progress or die are included regardless of duration of time on study treatment. This population will be used for supportive analyses of efficacy. Patients will be analyzed in the treatment arm to which they were randomized.

13.3.3. SVdX (Crossover from Vd) Population

The SVdX population consists of a subset of patients in the Vd Arm of the safety population who cross over from the Vd Arm to SVdX treatment after IRC confirmation of PD on Vd. This

population will be used specifically to analyze ORR1, PFS1, and safety information including Grade ≥2 peripheral neuropathy events.

13.3.4. SdX (Crossover from Vd) Population

The SdX population consists of a subset of patients in the Vd Arm of the safety population who cross over from the Vd Arm to SdX treatment after IRC confirmation of PD on Vd. This population is limited to patients who are unable to cross over to SVdX based on a newly-established and clearly documented intolerance to bortezomib while receiving treatment in the Vd Arm (eg, due to Grade >2 peripheral neuropathy or Grade ≥2 peripheral neuropathy with pain).

Disease response to SdX treatment will be assessed.

13.3.5. Safety Population

The safety population consists of all patients who receive at least 1 dose of study treatment. Patients will be analyzed according to the treatment they received. Additional safety cohorts may be defined to present results before and after patients randomized to the Vd Arm cross over to SVdX or SdX.

13.4. Data Analysis and Presentation

Summary tabulations will be provided for disposition, demographic, baseline, efficacy, and safety data as noted in the following sections. All data collected in the eCRF will be provided in by-patient data listings. Where appropriate, additional treatment groups, SVdX and SdX, will also be used to represent the data associated with Vd patients who cross over from the Vd Arm to SVdX or SdX after IRC-confirmed PD while patients were on Vd.

13.4.1. Procedures for Handling Missing Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the eCRF will be included in data listings that will accompany the clinical study report (CSR).

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For time to event analyses, patients who have no efficacy evaluations will be considered as censored at time 0.

For AEs, missing dates will be imputed per the rules outlined in the SAP. Each AE will be graded for severity according to NCI CTCAE v. 4.03. 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.

13.4.2. Patient Disposition

A tabulation of patient disposition will be presented, including the number screened, the number randomized, the number in each analysis population, the number of patients per randomized

stratification level, the number who discontinue treatment and reason(s) for treatment discontinuation, the number that withdrew from the study and reason(s) for study withdrawal, the number on treatment at the date of data cut-off, Durability of Response, and Survival Follow-up phase status.

13.4.3. Demographic Characteristics

Demographic characteristics will be summarized by treatment arm (SVd, Vd, SVdX, and SdX) and overall, and will include sex, race, ethnicity (Hispanic origin), and age at time of consent. For sex, race, ethnicity, the summary statistics will be the number and percentage of patients within each category. For age at time of consent, the mean, standard deviation, median, minimum, and maximum will be provided for each arm and the total sample. No formal hypothesis testing of treatment arm differences will be performed.

13.4.4. Baseline Characteristics and Medical History

Baseline characteristics include height, weight, BSA, ECOG performance status, and smoking history. If the Dubois (Dubois 1916) method for calculating BSA is entered by the site, BSA using the Mosteller (Mosteller 1987) method will be derived using the formula:

$$\text{BSA} = \text{Square Root } ([\text{Height(cm)} \times \text{Weight(kg)}]/3600).$$

A complete medical history (Section 11.2.2) will be obtained from each patient.

Medical history will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term. Baseline data will be summarized for each treatment arm using summary statistics; no formal hypothesis testing of treatment arm differences will be performed. Baseline symptoms will be listed only.

13.5. Efficacy Analysis

13.5.1. Primary Analysis for PFS

The PFS primary endpoint is defined as time from date of randomization until the first date of PD, per IMWG response criteria, or death due to any cause, whichever occurs first. PD for the primary PFS endpoint will be assessed centrally by the IRC (see Section 6.4). Clinical deterioration in the absence of objective M-protein increase is not considered PD. Patients who end study treatment due to clinical deterioration without an objective M-protein increase meeting the IMWG definition of PD will be censored for the PFS analysis. Unless specified otherwise, relapse from CR by positive immunofixation or trace amount (defined as less than 0.5 g/dL) of M-protein is not considered to be PD.

The primary analysis of PFS will be performed on the ITT population. The analysis will be repeated for the PP population as a supportive analysis.

PFS data will be summarized with KM methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs, as well as percentage of censored observations and proportion of events. Patients who remain progression-free (whether they withdraw from the study or reach their maximum follow-up) will be censored at the date of their last disease assessment. A stratified log-rank test will be used to compare the PFS distributions between treatment arms for the primary efficacy assessment; the strata will be those used for stratified

randomization. Hazard ratios will be estimated by a stratified Cox proportional hazards model with treatment as the only factor, the strata will be those used for stratified randomization. A non-stratified log-rank test and a Cox proportional hazards model will be used as sensitivity analyses.

Additional sensitivity analyses will be performed on the ITT population for the PFS primary endpoint as outlined below:

- Sensitivity Analysis #1: Events are defined as documented progression as verified by the IRC or death when the patient is closely followed, whichever occurs first. Patients are censored at the date of last disease assessment if no progression is confirmed by the IRC, treatment is discontinued for any reason, new anticancer treatment is started, or death or progression occurs after 2 or more missed visits.
- Sensitivity Analysis #2: Similar to the primary PFS endpoint analysis but where treatment discontinuation for any reason is counted as an event.
- Sensitivity Analysis #3: Similar to the primary PFS endpoint analysis but where the initiation of non-study antineoplastic therapy is counted as an event.
- Sensitivity Analysis #4: Similar to the primary PFS endpoint analysis but where clinical progression is counted as an event in addition to IRC-confirmed PD. Clinical progression is defined as the event when a patient discontinues the treatment with reason of PD but is not classified as PD by IRC.
- Sensitivity Analysis #5: Similar to the primary PFS endpoint analysis but where the timing of IRC-confirmed PD at an unscheduled visit is changed to the next scheduled visit.
- Comparison of PFS endpoint by treatment based on Investigator's assessment.

13.5.2. Analyses of the Key Secondary Endpoints

The following 3 endpoints, which are defined as key secondary endpoints, will be tested at the time of the second PFS IA according to the test sequence below:

1. ORR, defined as any response ≥PR (ie, PR, VGPR, CR, or sCR) based on the IRC's response outcome assessments, according to the IMWG response criteria
2. Incidence of any Grade ≥2 peripheral neuropathy events
3. Response rates for responses ≥VGPR based on the IRC's assessment

The hierarchical testing procedure will be used to maintain the overall Type I error of these 3 tests at a 1-sided 0.025 level of significance.

Statistical significance of the key secondary endpoints will not be claimed until the primary endpoint of PFS has reached significance.

13.5.2.1. Overall Response Rate

The secondary efficacy endpoint of ORR is defined as the proportion of patients who achieve a confirmed PR or better (ie, PR, VGPR, CR, or sCR) based on the IRC's response outcome assessments, according to the IMWG response criteria, before IRC-confirmed PD or initiating a

new MM treatment. All changes in MM disease assessments will be based on baseline MM disease assessments. ORR will be assessed on the ITT population at the time of the second PFS IA. The analysis will be repeated for the PP population as a supportive analysis.

Comparison of ORR between the 2 treatment arms will be performed using the Cochran Mantel Haenszel (CMH) test stratified by the randomization stratification factors. The Breslow-Day test will be used to evaluate the homogeneity of odds ratios across the strata associated with this endpoint. Patients missing post-C1D1 MM disease assessments will be imputed as non-responders.

A sensitivity analysis for ORR will be conducted on ITT patients where patients who have not had the opportunity to complete at least 2 post-C1D1 MM evaluations will be considered non-responders.

13.5.2.2. Incidence of Any Grade ≥2 Peripheral Neuropathy Events

The analysis for this safety endpoint is provided Section 13.7.1.1.

13.5.2.3. Response Rate for Responses ≥VGPR Based on the IRC's Assessment

The response rate for responses ≥ VGPR will be assessed on the ITT population at the time of the second PFS IA. The analysis will be performed in a similar manner to the secondary efficacy endpoint of ORR using the CMH test. The unadjusted number and percentage of patients will be summarized by treatment arm (SVd versus Vd) along with associated 95% CIs and the Breslow-Day test will be performed to assess homogeneity of odds ratios across the strata. Only responses ≥VGPR that occurred before IRC-confirmed PD or initiating a new MM treatment will be included in the analysis.

13.5.3. Analyses of the Non-Key Secondary Effiacy Endpoints

Brief summaries of the analyses for the non-key secondary efficacy endpoints are provided below. Additional details may be found in the SAP. These non-key secondary efficacy endpoints will be summarized by treatment arm for the ITT population, unless otherwise stated below or in the SAP.

- Overall survival: The analysis of OS will be performed by treatment arm (SVd versus Vd) based on the stratified log-rank test. The strata will be those used for stratified randomization. Median OS time with 95% CI will be estimated based on the KM method for each treatment arm. A sensitivity analysis will be performed for OS, in which patients will be censored at the date of first dose of the new anti-MM treatment.
- Response ≥CR, ≥sCR, or MRD negative (for patients who achieve CR or sCR): The number and percentage of patients with response ≥CR or response ≥sCR at any time prior to IRC-confirmed PD or initiating a new MM treatment will be summarized. The number and percentage of patients with MRD negative status at the time of response will be presented by treatment arm among those patients who achieve CR or sCR.

- Duration of response: The analysis of DOR will be performed as outlined for PFS above with statistical significance of the treatment group (SVd versus Vd) difference based on the stratified log rank test.
- ORR1: The analysis of ORR1 will be performed only on the SVdX patients. Patients who cross over from Vd to SdX after IRC-confirmed PD will not be included in the ORR1 analysis. The percentage of patients achieving a confirmed PR or better will be tested assuming a null hypothesis fixed threshold value of 10% against a 1-sided alternative hypothesis of >10% using exact methods for a 1-sample binomial without stratification. ORR1 will also be summarized with an associated 2-sided 95% CI.
- PFS1: The analysis of PFS1 will be performed only on the SVdX patients. The median PFS1 with 95% CI will be estimated based on the KM method.
- Time to next treatment (TTNT): TTNT analysis will be performed by treatment arm based on the stratified log-rank test. The strata will be those used for stratified randomization. Median TTNT with 95% CI will be estimated based on the KM method.
- Time to response (TTR): TTR analysis will be performed by treatment arm based on the stratified log-rank test. The strata will be those used for stratified randomization. The median TTR with 95% CI will be estimated based on KM method.
- PFS2 analysis will be performed for the patients who received post-SVd/Vd/SVdX treatment by treatment arm. The median PFS2 with 95% CI will be estimated based on KM method. The KM curve for PFS2 will be provided.
- Chemotherapy-induced Peripheral Neuropathy (QLQ-CIPN20): The actual value and change from baseline value before initiating a new MM treatment will be summarized by treatment arm using descriptive statistics over time for each of the 3 QLQ-CIPN20 subscale scores. Change from baseline will also be analyzed using a linear mixed effects model with treatment arm as the fixed effect, randomization stratification factors, and the baseline value of the corresponding subscale score as covariates, as well as random effect of patients and repeated measures over timepoints.

13.5.4. Exploratory Analyses

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13.6. Pharmacokinetic Analysis

The data obtained for PK evaluation will be assessed in several ways to determine if there are clinically relevant shifts in the PK of either study treatment. For bortezomib, the data will be subjected to a maximum a posteriori (MAP) Bayesian evaluation using the published steady-state model for this agent given as a single agent. Data from both arms will be evaluated in this fashion. Comparisons of the empirical Bayesian estimates of the clearance and derived AUC values for bortezomib given as a single agent may be conducted. In addition, a simulation of the expected time course of bortezomib may be generated and the observed bortezomib concentrations may be compared against the expected simulated concentration range.

For selinexor, a MAP analysis using a previously developed model for selinexor may be made and the resulting empirical Bayesian estimates compared with the historical results from single-agent studies. Similarly, the observed selinexor data may be compared with the expected simulated concentration ranges.

13.7. Safety Analysis

Safety analyses will be performed on the safety population, which includes all patients who receive at least 1 dose of study treatment. Patients will be analyzed according to the treatment they received.

13.7.1. Analysis of the Key Secondary Safety Endpoint

13.7.1.1. Peripheral Neuropathy Events

The analysis of the peripheral neuropathy events will be performed at the time of the second PFS IA. Statistical significance of peripheral neuropathy endpoint will not be claimed until PFS has reached significance.

Treatment differences for the incidence of any Grade ≥2 peripheral neuropathy events (the key secondary safety endpoint) will be tested using the Cochran-Mantel-Haenszel (CMH) test, stratified by the randomization stratification factors. The treatment difference will be assessed using the safety population. The number and percentage of patients will also be summarized by treatment arm (SVd versus Vd) along with the odds ratio and associated 95% CIs and the Breslow-Day test will be performed to assess homogeneity of odds ratios across the strata. A sensitivity analysis for the incidence of any Grade ≥2 peripheral neuropathy events will be conducted on the safety population where all Grade ≥2 peripheral neuropathy events that occur for Vd patients regardless of cross-over status will be included in the sensitivity analysis.

Similar analysis using the CMH test and the Breslow-Day test as described in Section 13.5.2 will be repeated to assess the incidence of any Grade peripheral neuropathy events on the safety population, as well as for Grades 2, 3, and 4 separately.

All peripheral neuropathy events may also be provided in a data listing.

13.7.2. Analyses of the Non-Key Secondary Safety Endpoints

13.7.2.1. Study Treatment Exposure

The following study treatment exposure data will be summarized: duration of exposure, number of cycles completed, percent compliance, dose intensity (defined as total study treatment received divided by duration of exposure, presented in mg/week and mg/day), number of missed doses, number of dose interruptions, duration of dose interruption, number of dose reductions, and number of dose escalations. Additional definition and analysis details may be found in the SAP.

13.7.2.2. Adverse Events

AEs will be coded using the MedDRA and displayed in tables and listings using MedDRA SOC and preferred term. The incidence rates of treatment-emergent AEs (TEAEs; separated by relationship to study treatment as assessed by the Investigator and maximum severity), SAEs, AEs of at least Grade 3 in severity using NCI CTCAE v. 4.03, treatment-related treatment-emergent SAEs, AEs leading to withdrawal of study treatment, and AEs leading to death will be summarized. TEAEs will be AEs that start or worsen on or after the first day dose of study treatment, through 30 days after the last dose, or any event considered treatment-related by the Investigator through the end of the study; related AEs will be AEs with an Investigator determination of related to treatment.

AEs with partial dates will be assessed using the available date information to determine if treatment-emergent using rules outlined in the SAP. AEs with completely missing dates will be

assumed to be treatment-emergent. No formal hypothesis-testing of AE incidence rates will be performed.

The causal relationship between the occurrence of an AE and the study treatment will be judged by the Investigator as not related or related (see Section 12.1.4). In the event a patient experiences repeat 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.

13.7.2.3. Clinical Laboratory Data

Clinical laboratory values will be expressed using conventional International System of Units (SI) units.

For each treatment arm, the actual value and change from baseline (Day 1, prior to the first administration of study treatment) to each on-study evaluation will be summarized for each quantitative clinical laboratory parameter, including, but not limited to, hematology, clinical chemistry, coagulation, and urinalysis. In the event of repeat values, the last non-missing value per study day 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 laboratory measures will be determined using NCI CTCAE criteria (eg, those measures that have a corresponding NCI CTCAE grade classification). Laboratory test results with NCI CTCAE Grades ≥3 will be presented in a by-patient data listing. Shift tables that present changes from baseline to worst on-study values and from baseline to last on-study values relative to NCI CTCAE classification ranges will be produced.

All laboratory data will be provided in by-patient data listings.

13.7.2.4. Vital Signs and Physical Examinations

The actual value and change from baseline (Day 1, prior to the first administration of study treatment) to each on-study evaluation will be summarized for vital signs including pulse rate, temperature, systolic BP, diastolic BP, weight, and BSA. Shift tables that present changes from baseline to worst on-study and last on-study ECOG performance status values will be produced.

Vital sign measurements and all physical examination findings will be presented in by-patient data listings.

13.7.2.5. Electrocardiogram

ECG results will be summarized descriptively, including heart rate and PR, QRS, QT, and QTc intervals (calculated by the Fridericia correction formula (Fridericia 1920); intervals. Actual values and changes from baseline will be reported for each study visit. ECG data for each patient will be provided in a by-patient data listing.

13.7.2.6. Ophthalmological Examinations

Ophthalmological examination findings will be summarized descriptively by visit and presented in by-patient data listings.

13.7.2.7. Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary and will be summarized by Anatomic Therapeutic Chemical Classification System level 2 (therapeutic level), level 4 (generic level), and standard names. Both prior and concomitant medications will be included in by-patient data listings.

13.8. QoL Analyses

Patient-reported peripheral neuropathy will be assessed using the EORTC-QLQ-CIPN20 validated instrument. The actual value and change from baseline will be summarized using descriptive statistics over time for each of the 3 EORTC-QLQ-CIPN20 subscale scores. Treatment differences in change from baseline to each scheduled visit will be evaluated using a linear mixed effects model with fixed effects of treatment arm, randomization stratification factors, and the baseline value for the parameter in the model as a covariate, as well as random effect of patients and repeated measures over time points.

CCI [redacted]

13.9. Changes in the Conduct of the Study or Planned Analyses

All deviations from the final SAP will be documented and provided in the final CSR.

14. ADMINISTRATIVE MATTERS

14.1. Regulatory and Ethical Compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC and United States Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

14.2. Ethics Committees

The protocol, the proposed ICF, and any other relevant records must be reviewed and approved by a properly constituted ethics committee (eg, IRB) before study start.

14.3. Regulatory Authority Approval

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

14.4. Protocol Adherence

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 the instructions and procedures found in this protocol. Investigators attest they will apply due diligence to avoid protocol deviations. All data points listed in this protocol and in the eCRFs are considered required. Any deviations from the protocol are to be recorded in the eCRF. 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 the Sponsor and approved by regulatory authorities where required, and the ethics committee (eg, IRB). Only amendments that are required for patient safety may be implemented prior to ethics committee (eg, IRB) 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, the Sponsor should be notified of this action, and the ethics committee (eg, IRB) at the study site should be informed according to local regulations but not later than 10 working days.

14.6. Informed Consent

Eligible patients may only be included in the study after providing written (witnessed, where required by law, ethics committee [eg, IRB], or regulation), ethics committee (eg, IRB)-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures. Note age on date consent is signed. Procedures that are part of the clinical routine evaluations during the initial diagnostic work-up of the patient may be performed before the ICF is signed and dated (ie, procedures that are not specific to the conduct of the study).

Informed consent must also be obtained for SVdX/SdX patients before conducting any study-specific procedures for SVdX/SdX treatment.

The process of obtaining informed consent should be documented in the patient source documents. A copy of the ICF must be given to the patient or to the person signing the form on behalf of the patient. The Investigator or designee must record the date when the study ICF was signed in the medical records of the patient. The name and role of the witness, if required, should also be documented.

The Sponsor will provide to Investigators, in a separate document, a proposed ICF that is appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the Investigator must be agreed to by Karyopharm before submission to the ethics committee (eg, IRB). If an ethics committee requests substantive changes to the ICF as part of their review, those revisions must also be submitted to Karyopharm for consideration prior to re-submission back to the IRB. A copy of the approved version must be provided to Karyopharm after ethics committee (eg, IRB) approval.

14.7. Patient Confidentiality and Disclosure

The Investigator must ensure anonymity of all patients; patients must not be identified by names in any documents submitted to Sponsor or its representative. Signed ICFs and patient enrollment logs must be kept strictly confidential.

14.8. Study Documentation, Data Collection and Storage, and Study Monitoring and Auditing Procedures

14.8.1. Study Documentation, Record Keeping, and Retention of Documents

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

Source data include all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

Data collection is the responsibility of the clinical study 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 is responsible for the accuracy, completeness, and timeliness of the data reported in the eCRFs and all other required reports. Data reported in the eCRFs, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested in the eCRF must be recorded. Any missing data must be explained. For eCRFs an audit trail will be maintained by the system.

The Investigator/institution should maintain study documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH GCP 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 15 years from the completion of the clinical study unless the 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. Study Monitoring and Auditing Procedures

A representative of Karyopharm will determine the adequacy of the facilities to perform the study in accordance with the protocol. These evaluations may occur before, at any time during, and/or after the study has been completed.

This study will be monitored in accordance with the ICH GCP E6 Section 5.18.4. The site monitor will perform visits to the study site at regular intervals.

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

During the study, when necessary, the Sponsor or its representatives, as well as regulatory authorities, must be permitted to review all study-related documents and other materials at the study site, including the Investigator Site File, study drug(s), and patients' original medical records/files.

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 major compliance or regulatory concerns arise, the Sponsor may conduct an audit without prior notice.

14.9. Disclosure of Information

All information provided to the Investigator by the Sponsor, or its representative, 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 the Sponsor, or its authorized representatives, or in confidence to the ethics committee (eg, 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 the Sponsor may terminate the Investigator's participation in this study after submission of a written notice. The Sponsor may terminate the study at any time upon immediate notice for any reason including the Sponsor's belief that termination of the study is necessary for patient safety.

14.11. Study Report and Publication Policy

Karyopharm assures that the key design elements of this protocol will be posted in a publicly accessible database such as www.clinicaltrials.gov. In addition, upon study completion and analysis of the resulting clinical data, the study will be:

- Reported to appropriate, competent regulatory authorities in full compliance with ICH E3: Structure and Content of Clinical Study Reports. A separate primary CSR may be prepared to summarize the results of the primary PFS analysis, followed by a final CSR after completion of the follow-up for all patients.
- Submitted for publication and/or posted in a publicly accessible database of clinical study results.

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APPENDIX 1. PROTOCOL AMENDENT: RATIONALES AND SUMMARY OF CHANGES

Amendment 3, Version 4.0

Summary of Changes

This primary reason for amending this protocol is to:

- Change ORR from a primary endpoint to a key secondary endpoint to address concerns expressed by the Agencies regarding including ORR as a primary endpoint (ie, an analysis of ORR could jeopardize the integrity of the study for the ultimate assessment of PFS).

The revised protocol Version 4.0 dated 17 August 2018 will be submitted 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 the key changes that were made to Version 3.0 of the protocol, including the rationale for these changes, in Version 4.0 is provided in the table below. Global changes or modification of large amounts of text are not described in detail, rather, a general description of the change is provided. When appropriate, exact changes to the text are provided. In these instances, ~~red font~~ indicates text that was deleted. Text that was added is provided in blue font.

Changes that were primarily editorial or administrative in nature or were made for readability and clarity are not detailed in the table.

Section(s)	Description of Change	Rationale for the Change
Global	Updated the version number and date to Version 4.0 and 17 August 2018 throughout to reflect the changes made in this version	Administrative
Global	Minor wording changes to improve clarity and conciseness.	Administrative
Protocol Approval Signature Page	Updated the approvers page to replace PPD MD, PhD with PPD MD, PPD PPD as a Sponsor signatory and to add MBA to PPD degrees	Administrative
Section 1: List of Abbreviations and Definitions of Terms	Updated the definition of Study Manual to include the Investigator Binder	Administrative
Section 4.2.4: Selinexor Metabolism/Drug-drug Interactions Section 4.2.6: Overall Clinical Experience with Selinexor	Updated the number of patients treated with selinexor to >2500 and the text to align with the Selinexor Investigator's Brochure v8.0 and NDA 212306 for accelerated approval of selinexor in triple class-refractory multiple myeloma (MM)	Administrative
Section 4.1.1: Disease Background Section 15: List of References	Updated the number of deaths from MM anticipated in 2018	Administrative
Section 1: List of Abbreviations and Definitions of Terms Section 4.2.1: Selinexor Mechanism of Action Section 4.2.2: Selinexor Pharmacodynamics and Dosing Frequency Section 4.2.3: Selinexor Pharmacokinetics	Updated the descriptions of the mechanism of action, PK, synergy with dexamethasone, and potential risks for selinexor and the data for Studies KCP-330-012 and KCP-330-017 to align with Selinexor IB v8.0 and the NDA 212306 for accelerated approval of selinexor in triple class-refractory MM	Administrative

Section(s)	Description of Change	Rationale for the Change
Section 4.2.5: Selinexor Nonclinical Combination with Dexamethasone and Proteasome Inhibitors Section 4.2.6: Overall Clinical Experience with Selinexor Section 4.2.6.1: Study KCP-330-017 (STOMP) Section 4.2.7: Potential Risks of Selinexor Section 15: List of References		
Section 14.5: Amendments to the Protocol	Revised the term "Health Authorities" to "regulatory authorities	Administrative
Section 14.8:Study Documentation, Data Collection and Storage, and Study Monitoring and Auditing Procedures Section 14.8.2: Study Monitoring and Auditing Procedures	Clarified study monitoring guidelines, combined the study monitoring subsection (14.12 in v3.0) with the auditing procedure subsection (Section 14.8.2) and revised the titles of Section 14.8 and Section 14.8.2.	Administrative
Section 15: List of References	Added a missing reference	Administrative
Section 3: Study Schematics and Schedule of Assessments and Dosing for Study KCP-330-023 (Table 3: Unique Visits Required for Crossover to SVdX or Sdx)	Revised the definition of "IRC-confirmed PD" in Table 3 and renamed the term as "IRC PD confirmation." Revised footnote b: ~~The IRC-confirmed PD date is the date of the first of the 2 consecutive assessments that meet the response criteria for PD, not the date~~ PD confirmation date is the date that the IRC informs the site that PD has been confirmed.	To clarify the start date of the 14-day window for the End of Vd Treatment Visits and C1D1 Visits for SVdX or SdX.

Section(s)	Description of Change	Rationale for the Change
Section 3.1 Schedules of Visits for In-clinic Dosing and MM Evaluations (Table 4: SVd Arm: Schedule of Visits for In-clinic Dosing and MM Evaluations) Section 6.1: Overall Study Design and Plan	Revised Note in Table 4: *Note: On C2D29 and C5D29, selinexor and dexamethasone dosing should be performed in the clinic PD during MM disease assessment visits. Revised sentence in Section 6.1: The Schedule of Assessments is provided in Table 2. Patients will have in-clinic visits for dosing of study treatment during MM evaluations (Table 13) and telephone contacts (Section 11.7.3).	To clarify that selinexor and dexamethasone dosing will occur in the clinic during MM disease assessment visits.
Section 1:List of Abbreviations and Definitions of Terms Section 4.2.7: Potential Risks of Selinexor Section 10.4.1: Selinexor Dose Reduction Guidelines (Table 16: Supportive Care and Selinexor Dose Adjustment Guidelines for AEs Related to Selinexor) Section 11.2.2: Medical History Section 12.1.2.3: Other Adverse Events Section 12.1.2.3.1: Tumor Lysis Syndrome (new subsection)	Added a description of the 8 tumor lysis syndrome (TLS) cases reported as of May 2018. The major change was the addition of Section 12.1.2.3.1. **Section 12.1.2.3.1. Tumor Lysis Syndrome** As of the date of this amendment, there have been 8 reports of TLS: 4 patients in Karyopharm-sponsored studies, 2 patients in Investigator-sponsored studies, and 2 patients in the expanded access program (compassionate use). Of the 8 patients, 5 had MM reported as their underlying cancer and 3 had hematological malignancies (including AML and acute lymphoblastic leukemia). The event onset latency ranged from 3 to 8 days (median 4 days). The total selinexor dose prior to event onset ranged from 40 to 320 mg (median 160 mg). The outcome was reported as recovered in 4 patients and not recovered in 2 patients; the outcome was not reported in 2 patients. The Investigators assessed 7 of the events as being related to selinexor. Of the 8 cases summarized above, there were 3 cases in which the patient died as a result of a TEAE. The cause of death in each of these cases was reported as: respiratory failure secondary to advanced MM, sepsis, and respiratory failure, chemotherapy induced cardiomyopathy and AML. No fatal outcomes due to TLS have been reported in any studies with selinexor, or in the ongoing	To update safety information for selinexor related to TLS.

Section(s)	Description of Change	Rationale for the Change
	EAP. Although the incidence of TLS is low (~0.3%), the causal relationship between selinexor treatment and TLS cannot be completely excluded. Early recognition of signs and symptoms in patients at risk for TLS, including identification of abnormal clinical and laboratory values, is key and Investigators must ensure that patients being treated with selinexor maintain adequate caloric and fluid intake. Close monitoring and management of patients with hematological malignancies, including MM, for potential signs and symptoms of TLS are most relevant. See Section 10.3 for supportive care and Table 16 for selinexor dose modification guidance. Related changes were made in the other sections noted.	
Section 2: Protocol Synopsis (including figure) Section 3: Study Schematics and Schedule of Assessments and Dosing for Study KCP-330-023 (Figure 1: Study KCP-330-023 Overview) Section 5.1.1: Primary Objective Section 5.1.2: Secondary Objectives Section 5.2.1: Primary Endpoint Section 5.2.2.1: Key Secondary Efficacy Endpoints Section 6.4: Independent Review Committee Section 13.2: Determination of Sample Size Section 13.2.1: Interim Analyses	1) Moved the comparison of ORR from a primary objective/endpoint to a key secondary endpoint and added a subsections for key secondary efficacy endpoints (Section 5.2.2.1) and for the analysis of ORR as a key secondary endpoint (Section 13.5.2.1). 2) Removed the split of the alpha level between PFS (0.02) and ORR (0.005) and added the assumed exponential dropout rate of 0.65% (Section 13.2). CCI [redacted] to the anticipated timing of the PFS IA prior to the completion of enrollment (Section 13.2.1.1). 5) Revised the definition of ORR to remove "from C1D1 of study treatment" (Section 5.2.2.1). **Section 5.1.1 Primary Objective~~s~~** • To compare PFS based on the IRC's disease outcome assessments in patients randomized to the SVd Arm versus the Vd Arm	1) and 2) The Agencies expressed concerns regarding including the ORR as a primary endpoint because an analysis of ORR could jeopardize the integrity of the study for the ultimate assessment of PFS. ORR was moved from a primary objective/endpoint to a key secondary endpoint to address these concerns. 3) The number of PFS events were re-estimate to reflect the recalculation due to the change in the alpha level (0.025). CCI [redacted]

Section(s)	Description of Change	Rationale for the Change
Section 13.2.1.1: Interim Analysis of PFS for Sample Size Re-estimation Section 13.2.1.2: Interim Analysis of PFS for Futility or Superiority Section 13.5.1.2: Primary Analysis for ORR (in v3) was deleted Section 13.5.2.1: Overall Response Rate (new) Section 14.11: Study Report and Publication Policy	~~• To compare the ORR (≥ PR) based on the IRC's response outcome assessments (Section 6.4), in patients randomized to the SVd Arm versus the Vd Arm~~ **Section 5.1.2 Secondary Objectives** • To compare the ORR (≥ PR) based on the IRC's response outcome assessments (Section 6.4), in patients randomized to the SVd Arm versus the Vd Arm • To compare the incidence of any Grade ≥2 peripheral neuropathy events ~~(total Grade ≥2 and separately for Grades 2, 3, and 4)~~ in patients randomized to the SVd Arm versus patients randomized to the Vd Arm • …… **Section 5.2.1 Primary Endpoint~~s~~** • PFS, defined as time from date of randomization until the first date of PD, per IMWG response criteria, or death due to any cause, whichever occurs first. For the purposes of PFS determination, PD will be determined by the IRC. ~~• ORR, defined as any response ≥ PR based on the IRC's response outcome assessments, according to the IMWG response criteria. All changes in MM disease assessments will be based on baseline MM disease assessments from C1D1 of study treatment.~~ **Section 5.2.2.1 Key Secondary Efficacy Endpoints** • ORR, defined as any response ≥ PR (ie, PR, VGPR, CR, or sCR) based on the IRC's response outcome assessments, according to the IMWG response criteria. All changes in MM disease assessments will be based on baseline MM disease assessments.	events have occurred, regardless of association with accrual status. 5) The definition of ORR was revised to align with the statistical analysis plan (SAP).

Section(s)	Description of Change	Rationale for the Change
	• Response rates at any time prior to PD or death due to any cause, pooled and separately for the following responses: ≥ VGPR, ≥ CR, ≥ sCR, or MRD negative (for patients who achieve CR or sCR) … **13.2.1.1 Interim Analysis of PFS for Sample Size Re-estimation** CCI [redacted]	

Section(s)	Description of Change	Rationale for the Change
	CCI [redacted]	

Section(s)	Description of Change	Rationale for the Change
	CCI [redacted]	
Section 2:Protocol Synopsis Section 5.1.2:Secondary Objectives Section 5.2.2: Secondary Efficacy Endpoints (new subsection) Section 5.2.2.2: Non-Key Secondary Efficacy Endpoints (new subsection) Section 13.5.2: Analyses of the Key Secondary Endpoints (new subsection) Section 13.5.3: Analyses of the Non-Key Secondary Efficacy Endpoints CCI [redacted]	1) Removed the secondary OS1 objective/endpoint. CCI [redacted] **Section 5.1.2 Secondary Objectives** … • To compare the DOR in patients randomized to the SVd Arm versus the Vd Arm • ~~To compare OS in patients randomized to the SVd Arm versus patients randomized to the Vd Arm who do not cross over to SVdX or SdX (Vd patients who cross over will be censored at the date of crossover) (OS1)~~ • ~~To compare ORR, PFS, and DOR for patients with 1 prior anti-MM regimen versus > 1 prior anti-MM regimen in patients randomized to the SVd Arm versus the Vd Arm~~ … CCI [redacted]	1) OS1 is now considered as a sensitivity analysis of OS, in which patients will be censored at the date of first dose of the new anti-MM treatment. 2) To align with the SAP.

Section(s)	Description of Change	Rationale for the Change
	CCI [redacted]	
Section 2: Protocol Synopsis Section 5.2.2.2: Non-Key Secondary Efficacy Endpoints (new subsection)	Revised the definition of DOR to specify "IRC-confirmed" response and death "due to any cause." • DOR, defined as the duration of time from first occurrence of IRC-confirmed response ≥ PR until the first date of IRC-confirmed PD or death due to any cause, whichever occurs first	To align with the SAP
CCI [redacted]	CCI [redacted]	1) These endpoints are discussed in the SAP as subgroup analyses of PFS and ORR but are not considered to be separate endpoints. 2) To align with the more accurate language in the SAP.

Section(s)	Description of Change	Rationale for the Change
	CCI [redacted]	
Section 2: Protocol Synopsis Section 6.1: Overall Study Design and Plan Section 8.2: Randomization to Study Treatment	Revised the basis for the determination of R-ISS stage used in stratification of randomization from "at original MM diagnosis" to "at study entry, based on screening results." **Section 8.2 Randomization to Study Treatment** … Randomization will be stratified based on the following stratification factors and will maintain the 1:1 allocation between treatment arms (SVd, Vd) within each of the stratification categories: • Prior PI therapies (Yes or No) • Number of prior anti-MM regimens (1 versus >1)	To provide the correct basis for determination of R-ISS stage.

Section(s)	Description of Change	Rationale for the Change
	• R-ISS stage at ~~original MM diagnosis~~ study entry, based on screening results (R-ISS Stage III versus R-ISS Stage I or II) (Palumbo 2015). If data for chromosomal abnormalities (CA) and serum lactate dehydrogenase (LDH) required for R-ISS staging are not available, patients will be assigned to the R-ISS category corresponding to their ISS stage. … Related changes were made in Section 6.1.	
Section 6.1: Overall Study Design and Plan Section 6.2: Crossover	Added an exception to the requirement that patients will either remain on study treatment until PD is confirmed by the IRC or discontinue study treatment, complete the EoT Visit, and be followed for survival. The exception only applies to patients in the Vd Arm who must terminate bortezomib prior to IRCconfirmed PD due to significant toxicities. **Section 6.2 Crossover** … The following process will be used in order to prevent premature crossover: 1. Investigators will assess PD according to the IMWG criteria including repeat testing if PD is based on serum and/or urine M-protein, quantitative immunoglobulins for IgA/IgD, or serum free light chain (FLC). PD may also be based on new or enlarging plasmacytoma(s) or bone lesion(s) or on other symptoms and signs of clinical progression that meet the IMWG criteria. 2. All cases of PD must be confirmed by the IRC prior to crossover.	To give patients in the Vd Arm who must terminate bortezomib prior to IRC-confirmed PD due to significant toxicities an opportunity to receive selinexor.

Section(s)	Description of Change	Rationale for the Change
	3. Crossover will not be permitted based purely on Investigator-assessed progression that does not meet any IMWG criteria for PD and cannot be verified by IRC (eg, deteriorating performance status). 4. Crossover will not be permitted if dosing of bortezomib is terminated before PD is confirmed by the IRC, unless termination of bortezomib is due to significant toxicities such as peripheral neuropathy, and all treatment measures addressing these toxicities are exhausted and documented prior to bortezomib termination. Early termination of bortezomib should be discussed and approved by the Sponsor Medical Monitor in order to allow crossover to SdX after progression is confirmed by the IRC. 5. Investigator-assessed presumptive PD events that are not confirmed by the IRC will have their PFS censored at the time of treatment discontinuation. --- Related changes were made to the other sections noted.	
Section 6.3: Data Safety Monitoring Board	Added a more detailed description of the Data Safety Monitoring Board (DSMB). **Section 6.3 Data Safety Monitoring Board** An independent Data Safety Monitoring Board (DSMB) will be set up for the study to review safety data for this study. ~~The DSMB will review safety data at intervals outlined in the DSMB charter.~~ The DSMB is made up of a group of individuals with pertinent expertise that reviews, on a predetermined schedule, safety data from this clinical study. It is the DSMB's responsibility to weigh risks and benefits throughout the study's duration. The DSMB will provide oversight and safety monitoring of the study in	To align with the DSMB charter

Section(s)	Description of Change	Rationale for the Change
	compliance with applicable regulations, legislation and associated guidance materials for the nature of the study. As appropriate, ~~T~~the DSMB will provide recommendations to the Sponsor regarding continuation, modification, or discontinuation of the study based on ~~the safety results~~ its assessment of the reviewed safety data. This DSMB will be composed of 4 voting members (3 oncologists and an independent statistician) a Chairperson and 3 voting members who will review safety data from the study. The DSMB membership, functioning, and procedures are described in the DSMB charter.	
Section 3: Study Schematics and Schedule of Assessments and Dosing for Study KCP-330-023 (Table 2: Schedule of Assessments for Study KCP-330-023, footnote p) Section 7.2: Inclusion Criteria Section 10.8.1: Contraception Requirements Section 12.3.1: Pregnancy and Breastfeeding	Revised inclusion criterion #12, contraception requirements, and guidance for pregnancy and breastfeeding. **Section 7.2 Inclusion Criteria** … 12. 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. Female patients of childbearing potential and fertile ~~M~~male patients who are sexually active with a female of childbearing potential must use ~~an~~ highly effective ~~barrier~~ methods of contraception ~~if sexually active with a female of childbearing potential. For both male and female patients, effective methods of contraception must be used~~ throughout the study and for 3 months following the last dose of study treatment. Highly effective methods of contraception are listed in Section 10.8.1. **Section 10.8.1 Contraception Requirements** Patients should not become pregnant or father a child while on this study because the study treatments in this	To align with the highly effective methods and pregnancy/breastfeeding guidance described in the new safety language template provided by the Karyopharm Pharmacovigilance Department

Section(s)	Description of Change	Rationale for the Change

	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 and fertile male patients must agree to use ~~2 methods of~~ highly effective 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~~ listed below (ie, results in a low failure rate when used consistently and correctly) during the dosing period and for a period of at least 3 months after the end of treatment.
	Highly effective methods include:
	• ~~Hormonal contraceptives (e.g., combined oral contraceptives, patch, vaginal ring, injectables, and implants)~~
	• combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
	  ○ oral
	  ○ intravaginal
	  ○ transdermal
	• progestogen-only hormonal contraception associated with inhibition of ovulation:
	  ○ oral
	  ○ injectable
	  ○ implantable
	• ~~I~~intrauterine device ~~or~~
	• intrauterine hormone-releasing system	

Section(s)	Description of Change	Rationale for the Change
	~~• Vasectomy or tubal ligation~~ • bilateral tubal occlusion • vasectomized partner • sexual abstinence ~~Effective methods include:~~ • ~~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:~~	

Section(s)	Description of Change	Rationale for the Change
	• ~~A sexual partner who is permanently 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. 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 4.2.7.1 for additional safety information related to pregnancy. **Section 12.3.1 Pregnancy and Breastfeeding** Note: Pregnancy per se is not considered to be an AE; however, it is discussed here because of the importance of reporting pregnancies that occur during studies and because a medical occurrence observed in the mother or fetus/newborn would be classified as an AE. ~~To ensure patient safety, a pregnancy occurring while the patient is on study treatment must be reported to Karyopharm Pharmacovigilance by email or fax within 24 hours of first knowledge of its occurrence. A pregnancy report form is provided by Karyopharm.~~ Female patients of childbearing potential and fertile male patients will be informed as to the potential risk of conception while participating in this study and will be advised that they must use highly effective contraception	

Section(s)	Description of Change	Rationale for the Change
	listed in Section 10.8.1 (ie, results in a low failure rate when used consistently and correctly) during the dosing period and for a period of at least 3 months after the end of treatment. A pregnancy test will be performed on each premenopausal female patient of childbearing potential prior to the first dose of study drug, on Day 1 of Cycles ≥2 while on treatment, and again at treatment discontinuation during the End-of-Treatment visit. A negative pregnancy test must be documented prior to administration of study drug. If a patient is confirmed pregnant during the study, study drug administration must be discontinued immediately. The Investigator must immediately notify the Sponsor's Medical Monitor of the event and record the pregnancy on the Pregnancy Form (provided by Karyopharm). The initial information regarding a pregnancy must be forwarded to Karyopharm's Pharmacovigilance by email or fax within 24 hours of first knowledge of its occurrence. The pregnancy should be followed up to determine the outcome, including spontaneous or voluntary termination, details of the birth, and any birth defects, congenital abnormalities, or maternal and/or newborn complications. ~~Pregnancies must be reported to Karyopharm, regardless of whether the patient withdraws from the study or the study is completed, for 3 months after the patient receives his/her last dose of study treatment. Patients should be instructed~~ to inform the Investigator regarding any pregnancies. All pregnancies occurring within 3 months after the patient's last dose of study drug must be reported to Karyopharm, regardless of whether the patient received selinexor or other study drugs, withdraws from the study,	

Section(s)	Description of Change	Rationale for the Change
	or the study is completed. Patients should be instructed to inform the Investigator regarding any pregnancies. Any SAE that occurs during pregnancy must be recorded on the SAE report form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (described in Section 12.2.3). A pregnancy in a female partner of a male patient must be reported to Karyopharm within 24 hours of learning of its occurrence. Pregnancies in female partners should only be followed if the male patient is being treated with a selinexor-containing regimen. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner. It is not known whether selinexor passes into the breast milk. Mothers should not breastfeed while being treated with selinexor-containing regimen.	
Section 10.2.3.2: Selinexor	Clarified the wording for how selinexor should be administered and removed the need to take selinexor with food. Selinexor tablets should be taken ~~with food, or within 30 minutes after the patient has eaten, together~~ orally with at least 120 mL (4 ounces) of ~~fluids~~ water at approximately the same time each day. It can be taken with or without food. Selinexor tablets should be swallowed whole (not crushed) to prevent an increased risk of dermatologic toxicity if the powder comes in contact with skin.	To align with the guidance in the current Selinexor Investigator's Brochure (IB)

Section(s)	Description of Change	Rationale for the Change
Section 10.5.1: Missed Doses of Study Treatments (Selinexor, Bortezomib, and Dexamethasone)	Revised the guidance for doses of study treatment that must be missed due to protocol- or study-related reasons to: 1) Provide 72 hours between 2 consecutive doses of bortezomib 2) Remove the requirement for 36 hours between doses **Section 10.5.1 Missed Doses of Study Treatments (Selinexor, Bortezomib, and Dexamethasone)** Missed doses of ~~all~~ study treatments should be managed as follows: For doses missed for protocol- or study-related reasons (eg, due to recommendation of the Investigator, such as due to an AE): • ~~**If a dose was missed**, the schedule of that week should be altered to accommodate 2 doses in that week with at least 36 hours between 2 consecutive doses.~~ • ~~**If a dose must be skipped** (e.g., due to recommendation of the Investigator), 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.~~ • **Missed dose of bortezomib for patients in the Vd Arm Only:** If a bortezomib dose was missed, the schedule of that week should be altered to accommodate 2 doses in that week with at least 72 hours between 2 consecutive doses of bortezomib. • **Missed dose of any study treatment for all patients:** If a dose of any study treatment must be missed, the next dose will be taken as per schedule. All missed and delayed doses should be documented.	1) To provide 72 hours between 2 consecutive doses of bortezomib in a week for patients in the Vd Arm as required in the Velcade® Prescribing Information 2) To clarify that the next dose for study treatments missed due to protocol- or study-related reasons should be taken per schedule and to remove the requirement for 36 hours between doses

Section(s)	Description of Change	Rationale for the Change
	For doses missed for reasons not related to the protocol/study (eg, a required medical procedure or an unanticipated personal emergency): • If a patient missed a full 1- or 2-week period of study treatment dosing for events that are not related ~~(e.g., a required medical procedure or an unanticipated personal emergency),~~ to the protocol or the study the days missed will be replaced. For example, if a patient missed C2D7 to C2D14, then the patient will start the next dosing on C2D7 following the break. Similarly, if a patient misses C3D1 to C3D15, then the patient will start the next dosing on C3D1. The schedule of MM evaluations will be maintained regardless of drug holidays or drug interruptions (Section 11.3.1).	
Section 10.3.3: Infection Section 10.4.1: Selinexor Dose Reduction Guidelines (Table 16: Supportive Care and Selinexor Dose Adjustment Guidelines for AEs Related to Selinexor) Section 10.4.1.1: Selinexor Dose Adjustment in the Setting of Infection	Updated the supportive care instructions for consistency with current clinical practice.	To align with the guidance in the current Selinexor IB
Section 10.8.3.1: Restrictions for Selinexor	Deleted the restriction for alcohol use on study treatment dosing days.	To align with the guidance in the current Selinexor IB
Section 3: Study Schematics and Schedule of Assessments and Dosing for Study KCP-330-023 (Table 2: Schedule of	Added text in a new subsection (Section 11.4.2.1) to indicate that a portion of the bone marrow aspirate will be collected to isolate plasma, non-tumor CD138- and tumor CD138+ cell fractions for subsequent PDn studies. **Section 11.4.2.1 Bone Marrow Aspirates for PDn**	To obtain samples to be used in analyses to identify predictive biomarkers of selinexor response, characterize the knowledge of selinexor's mechanism of action, and/or assess the presence of the high risk mutations.

Section(s)	Description of Change	Rationale for the Change
Assessments for Study KCP-330-023, footnote v) Section 11.3.1.9: Bone Marrow Aspirate Section 11.4.2 Pharmacodynamic Studies (new) Section 11.4.2.1: Bone Marrow Aspirates for PDn (new)	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's mechanism of action. 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 and chromosome 1q21 amplification. 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. Details of PDn sample collection and processing can be found in the Study Manual. Related changes were made to the other sections noted.	
Section 3: Study Schematics and Schedule of Assessments and Dosing for Study KCP-330-023	Removed the North American restriction for PK sampling.	To provide flexibility for PK sampling to be performed at selected sites outside of North America

Section(s)	Description of Change	Rationale for the Change
(Table 2: Schedule of Assessments for Study KCP-330-023, PK row and footnote q) Section 11.4.1: Pharmacokinetic Endpoints		
Section 1:List of Abbreviations and Definitions of Terms Section 11.5.1.4: Ophthalmic Examination	Added the specific grading system (ie, the American Optometric Association) for cataract/lens opacity. **Section 11.5.1.4 Ophthalmic Examination** … If a cataract/lens opacity is seen during the examination, the cataract/lens opacity will be graded according to ~~a Grade 1 to 4 system~~ the American Optometric Association (AOA) Cataract Grading System, which is available on the AOA website (www.aoa.org).	To provide the specific grading system (ie, the American Optometric Association) that will be used to assess cataract/lens opacity
Section 12.1.2: Recording of Adverse Events Section 12.1.2.1 Laboratory Test Abnormalities Section 12.1.3: Adverse Event Severity Section 12.2.2: Recording of Serious Adverse Events	Made minor wording changes to the guidance in these sections for clarity.	To align with the new safety language template provided by the Karyopharm Pharmacovigilance Department
Section 12.2: Serious Adverse Event Section 12.2.1: Events that Do Not Meet the Definition of a Serious Adverse Event	Added a new subsection (Section 12.2.1) with text clarifying the definition of events that do not meet the definition of an SAE. **Section 12.2.1 Events that Do Not Meet the Definition of a Serious Adverse Event**	To align with the definition of SAEs described in the new safety language template provided by the Karyopharm Pharmacovigilance Department

Section(s)	Description of Change	Rationale for the Change
	~~Hospitalizations for elective surgery or other medical procedures that are not due to an AE are not considered SAEs. A hospitalization meeting the regulatory definition for 'serious' is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. An emergency room visit is not considered a hospitalization unless it results in an official admission to the hospital.~~ Elective hospitalizations to administer, or to simplify study treatment or study procedures (ie, an overnight stay to facilitate 24-hour urine collection) or other medical procedures are not considered SAEs. A 'serious' hospitalization is defined as any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. An emergency room visit is not considered a hospitalization unless it results in an official admission as an inpatient to the hospital (eg, undesirable effects of any administered treatment) and must be documented as an SAE. Progression of the malignancy/disease (including fatal outcomes) should NOT be reported as an SAE during the study or within the safety reporting period (see Section ~~12.2.2~~ 12.2.3). Sudden or unexplained death should be reported as an SAE. If there is any uncertainty about a finding being due solely to progression of malignancy/disease, the finding should be reported as an AE or SAE, as appropriate.	
Section 12.3.2: Overdose, Abuse, Misuse, Medication Errors, and Occupational Exposure Section 12.3.2.1: Overdose Section 12.3.2.2: Abuse, Misuse, or Medication Error	Changed the reporting mechanism for reporting overdose, abuse, misuse, medication errors, and occupational exposure from fax to email. Revised the timing for reporting of overdose, abuse, misuse, medication errors, and occupational exposure for events that are not AEs or SAEs from "as soon as possible" to "within 24 hours of awareness."	To align with the guidance described in the new safety language template provided by the Karyopharm Pharmacovigilance Department

Section(s)	Description of Change	Rationale for the Change
Section 12.3.2.3: Occupational Awareness	Added the following to Section 12.3.2.1 Overdose: As selinexor is metabolized by GSH conjugation, it is possible, but not demonstrated, that hepatic GSH depletion might occur in case of extreme overdose. Therefore, in overdose cases, if patients develop liver function test abnormalities, supportive measures such as SAM or other drugs that can replace GSH might be considered as part of the overall management plan.	
Section 2: Protocol Synopsis Section 5.2.2.1: Key Secondary Efficacy Endpoints (new subsection) Section 5.2.2.2:Non- Key Secondary Efficacy Endpoint (new subsection) Section 5.2.3.1: Key Secondary Safety Endpoint (new subsection) Section 13.5.2: Analyses of the Key Secondary Endpoints (new subsection) Section 13.5.2.1: Overall Response Rate (new subsection) Section 13.5.2.2: Incidence of Any Grade ≥2 Peripheral Neuropathy Events (new subsection) Section 13.5.2.3: Response Rate for Responses ≥VGPR Based on the IRC's Assessment (new subsection)	1) Moved OS from a key secondary efficacy endpoint to a non-key secondary efficacy endpoint. 2) Added ORR as the second key secondary efficacy endpoint. 3) Moved response rates for responses ≥ VGPR from #2 to #3 (to replace OS). Key secondary endpoints are as follows:1. ORR, defined as any response ≥ PR (ie, PR, VGPR, CR, or sCR) based on the IRC's response outcome assessments, according to the IMWG response criteria.; 2. Incidence of ~~all grades and~~ any Grade ≥2 peripheral neuropathy events; 3. Response rates for responses ≥ VGPR based on the IRC's assessment. 4) Created subsections for Key Secondary Efficacy Endpoints (Section 5.2.2.1), the Key Secondary Safety Endpoint (Section 5.2.3.1), Analyses of the Key Secondary Endpoints (Section 13.5.2), and Analyses of the Non-Key Secondary Efficacy Endpoints (Section 13.5.3). 5) CCI	1) OS was moved from a key secondary endpoint to a secondary endpoint because the expected median OS for patients with MM following ≥1 prior therapy is ~ 5 years and, consequently, only a small number of death events are expected to occur by the time of the final PFS analysis. 2) ORR was moved from a primary to a key secondary endpoint to address concerns expressed by the Agencies about using ORR as a primary endpoint (ie, an analysis of ORR could jeopardize the integrity of the study for the ultimate assessment of PFS). 3) Response rates for responses ≥ VGPR were moved from #2 to #3 to replace OS. 4) and 5) Descriptions of the analyses were revised to align with the SAP.

Section(s)	Description of Change	Rationale for the Change
Section 13.5.3: Analyses of the Non-Key Secondary Efficacy Endpoints (new subsection) CCI Section 13.7.1.1: Peripheral Neuropathy Events (new subsection)		
Section 13.5.3: Analyses of the Non-Key Secondary Efficacy Endpoints (new subsection)	Removed the following from the analysis of the secondary endpoint of ORR1: "It is expected that approximately 70 patients will cross over from the Vd Arm to SVdX. CCI	Power is irrelevant for a secondary endpoint
CCI	CCI	
Section 13.5.1: Primary Analysis for PFS	1) Added the following definition of clinical progression to sensitivity analysis #4: Similar to the primary PFS endpoint analysis but where clinical progression is counted as an event in addition to IRC confirmed PD. Clinical progression is defined as the event when a patient discontinues the treatment with reason of PD but is not classified as PD by IRC. 2) Added the following sensitivity analysis: Comparison of PFS endpoint by treatment based on Investigator's assessment.	1) To provide a definition of clinical progression for clarity 2) To further evaluate the robustness of the primary endpoint analysis results
Section 13.7.2.7: Concomitant Medications	Revised the description of the Anatomic Therapeutic Chemical Classification System summaries.	To align with the SAP

Section(s)	Description of Change	Rationale for the Change
	Section 13.7.2.7 Concomitant Medications Concomitant medications will be coded using the World Health Organization Drug Dictionary and will be summarized by Anatomic Therapeutic Chemical Classification System ~~3~~ level 2 (therapeutic level), level 4 (generic level), and standard ~~preferred~~ names. Both prior and concomitant medications will be included in by-patient data listings.	

Amendment 2, Version 3.0

Amendment Rationale

The primary purpose for this amendment is to incorporate changes the statistical analysis sections to address comments from the FDA received on 04 April 2017.

Other changes include:

- Additional pregnancy testing and a clarification to contraception requirements to align with the recommendations of the Clinical Trial Facilitation Group
- Details for continuation of study treatment for patients if the study is terminated early to comply with ICH GCP E6

The revised protocol Version 3.0 dated 06 April 2017 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards, Independent Ethics Committees, or Research Ethics Boards, and by Karyopharm Therapeutics Inc. to all applicable regulatory authorities.

A summary of the changes that were made to Version 2.0 of the protocol in Version 3.0 is provided below.

Changes to the protocol

Administrative

- Updated the version number and date to Version 3.0 and 06 April 2017 throughout to reflect the changes made in this version (**Modified sections:** Global).
- Revised "> Grade X" to "Grade > X" and "≥ Grade X" to "Grade ≥ X" (**Modified sections**: Global).
- Revised the first signatory to the Chief Executive Officer and Acting Chief Medical Officer (**Modified section**: Signature Page).
- Made minor editorial changes to the supportive care table **(Modified section**: Table 15).

Randomization

- Added details for the Interactive Response Technology system that will be used to perform treatment randomization to address the FDA request to include a randomization method in the protocol (**Modified section**: 8.2).

Early Termination of the Study

- Added details for continuation of study treatment for patients if the study is terminated early to comply with ICH GCP E6 (**Modified section:** Section 9.1).

Contraception Requirements

- Clarified that double-barrier contraception methods are considered effective but not highly effective to align with the recommendations of the Clinical Trial Facilitation Group. Revised text: "A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable (ie,

effective), but not highly effective, birth control methods." Also clarified that sexual partners who are surgically sterilized are not exempt from the contraception requirements unless they are "permanently" surgically sterilized (**Modified section:** Section 10.8.1).

Schedule of Assessments

- Added the requirement for pregnancy testing (serum hCG or urine) for females of childbearing potential prior to dosing on Day 1 of Cycles ≥2 to align with the recommendations of the Clinical Trial Facilitation Group (**Modified sections:** Section 11.5.2.2 and Tables 2 and 12).

Efficacy Analysis

- For the PFS primary efficacy endpoint, changed the analysis to stratified log-rank test and stratified Cox model (previously in Version 1.0 of the protocol) to address the FDA request to explain why the stratification factors were removed. Also, specified that the stratified log-rank test will be used for the secondary analyses of OS, DOR, and OS1 CCI [redacted] will be performed using stratified log-rank test (**Modified sections**: Sections 13.5.1.1, 13.5.2, and 13.5.3).
- For the ORR efficacy analysis, specified that patients missing post-C1D1 MM disease assessments will be imputed as non-responders to address the FDA comment that patients missing ORR assessment should be imputed as non-responders (**Modified section**: Section 13.5.1.2).
- Changed the timing of the secondary analyses from "after significance is reached for PFS" to "at the time of ORR analysis" and specified that "statistical significance of secondary endpoints will not be claimed until ORR and PFS have reached significance." This change was made to address the FDA request to specify how the alpha will be allocated for the secondary endpoint if the ORR result is significant, but the PFS secondary interim analysis result does not cross the boundary (**Modified section**: Section 13.5.2).

Changed the Hochberg procedure for testing the secondary endpoints to a hierarchical testing procedure to address the FDA recommendation to use a hierarchical testing procedure for the secondary endpoints. Per the FDA, the Hochberg procedure is not an assumption-free method. Although it provides adequate overall alpha-control for independent and for certain types of positively correlated endpoints, its properties for other types of dependent endpoints are not fully known (**Modified sections**: Sections 13.5.2 and 15).

Amendment 1, Version 2.0

Amendment Rationale

The primary purpose for this amendment is to incorporate changes to address comments from the FDA received on 05 January 2017. The majority of these changes, as detailed below, were made to the efficacy analysis and the background and administrative sections.

The revised protocol Version 2.0 dated 22 February 2017 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards, Independent Ethics Committees, or Research Ethics Boards, and by Karyopharm Therapeutics Inc. to all applicable regulatory authorities.

A summary of the changes that were made to Version 1.0 of the protocol in Version 2.0 is provided below.

Changes to the protocol

Administrative

- Updated the version number and date to Version 2.0 and 22 February 2017 throughout to reflect the changes made in this version (**Modified sections:** Global).
- Removed Section 1 (Sponsor Information) because the information was redundant and renumbered the sections globally (**Modified sections:** Global).
- Internal changes to improve clarity and eliminate inconsistencies between sections (**Modified sections**: Global).
- Revised color of active links ie, (numbers for sections and table/figure links) to blue font to align with new medical writing practices (**Modified sections**: Global).
- Revised the first signatory to the Senior Vice President of Clinical development (**Modified section**: Signature Page).
- Removed details for the statistical analyses from the Synopsis (**Modified section**: Synopsis).
- Updated the list of abbreviations and added the definition of Study Manual to improve clarity (**Modified section**: Table 1).
- Corrected footnote #7 in Table 2 to provide C10D29 as an example of an in-clinic dosing visit on which the window for MM disease assessments may be extended (**Modified section**: Table 2).
- Clarified that the End of Vd Treatment Visit and the C1D1 Visit for SVdX or SdX Treatment may be combined at the discretion of the Investigator. Also clarified that the IRC-confirmed PD date is the date of the first of the 2 consecutive assessments that meet the response criteria for PD, not the date that the IRC informs the site that PD has been confirmed (**Modified section**: Table 3).
- Removed Figure 2, which contained redundant information for MM disease assessments and the dosing scheme (**Modified sections**: Section 6.1 and Figure 2).

- Expanded the introduction section to include additional justification for the proposed dosing regimen to address the FDA request to add adequate justification of the proposed dosing regimen in the protocol, including PK, PDn, nonclinical, efficacy, and safety data (**Modified sections:** Sections 4.2.5, 4.2.6.1, and 4.3; **New Sections**: 4.2.2, 4.2.3, 4.2.4, 4.4.2, and 4.4.2.1).
- Updated clinical study data for clinical experience with selinexor (**Modified sections:** Sections 4.2.6 and 4.2.6.1).
- Removed the use of a Patient Enrollment Form to reflect the electronic enrollment process that is being used for this study (**Modified section**: Section 8.1).
- Minor wording changes to improve clarity related to dosing information for bortezomib and dexamethasone (**Modified sections**: Sections 10.2.3.3, 10.2.3.4, 10.4.3, 10.8.3.2, and 10.8.4).
- Added a separate subsection (Section 10.2.6) for duration of treatment and follow-up (**Modified section:** Section 10.2).
- Corrected footnote #1 in Table 14 to indicate that patients who are tolerating SVd well may be dose escalated to correct a typographical error (**Modified section**: Table 14).
- Removed the following sentence, which is not accurate from the missed doses section: “In this fashion, laboratory and radiographic assessments remain appropriate for timing of the administration of anticancer therapy” (**Modified section:** Section 10.5.1).
- Added note regarding contact information for urgent medical issues (**Modified section:** Section 12).
- Moved section for Procedures for Handling Missing Data from the Safety Analysis section to the appropriate location in the Data Analysis and Presentation section (**Modified sections**: Sections 13.4.1 and 13.7).
- Revised references to Endnote format to align with new medical writing practices. (**Modified section**: Section 15).

Study Design

- Added crossover to treatment with selinexor and dexamethasone (SdX) as an option for patients in the Vd Arm after PD is confirmed by the IRC if they have significant tolerability issues with bortezomib (eg, Grade >2 peripheral neuropathy or Grade ≥2 peripheral neuropathy with pain). This change was made to provide access to selinexor treatment for patients randomized to the Vd Arm who are unable to tolerate continued treatment with bortezomib after PD is confirmed (**Modified sections:** Synopsis, Sections 4.4.1, 5.1.2, 5.1.3, 5.2.2.1, 5.2.3, 6.1, 6.2, 6.4, 9.2, 9.3, 10.2.4, 11.1, 11.3.1, 11.7.3, 11.7.4, 13.3.5, 13.4, 13.4.3, 14.6, and Tables 2 and 3, and Figure 1; **New sections:** Sections 13.3.3 and 13.3.4 and Tables 7 and 11.

Objectives/Endpoints

- Changed the third key secondary efficacy objective/endpoint from DOR to OS to address the FDA request to remove the key secondary efficacy endpoint of DOR. DOR is being replaced because it is not acceptable as a regulatory endpoint for inferential purposes for an analysis that is based on a nonrandomized subgroup. (**Modified sections:** Synopsis and Sections 5.1.2, 5.1.3, 5.2.2.1, 5.2.3, and 13.5.2).
- CCI
- Revised the definition of time to response to "the duration of time from randomization to the first documented response (≥ PR) per IMWG response criteria" to address the FDA request to revise the starting point for time to response to "time from randomization" (**Modified section:** Section 5.2.2.1).

IMWG Response Criteria

- 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 (**Modified sections:** Synopsis; Sections 5.0, 7.2, 11.3.1, and, Table 16).

Crossover

- Clarified points 1 and 3 of the process that will be used to prevent premature crossover. For point 1, Investigators will also assess PD on other symptoms and signs of clinical progression that meet the IMWG criteria. For point 3, crossover will not be permitted based purely on Investigator-assessed progression that does not meet any IMWG criteria for PD and cannot be verified by IRC (eg, deteriorating performance status). Also revised "putative PD" in point 5 to "Investigator-assessed presumptive PD to clarify the meaning of "putative PD" as requested by the FDA (**Modified section:** Section 6.2).

Exclusion Criteria

- Made minor wording changes to exclusion criteria 1 and 11, as follows, to align standard text across protocols (**Modified section:** Section 7.3):
  - Criterion 1 changed from "Has received selinexor or another XPO1 inhibitor previously" to "Prior exposure to a SINE compound, including selinexor."
  - Criterion #11 changed from "Intolerance, hypersensitivity, or contraindication to glucocorticoids" to "Known intolerance, hypersensitivity, or contraindication to glucocorticoids."

- Revised exclusion #12 to clarify that patients treated with an investigational anticancer therapy within 2 weeks prior to C1D1 are specifically excluded from the study (**Modified section:** Section 7.3).

Schedule of Assessments

- Clarified that symptom-directed physical examinations will only be performed if clinically indicated to address questions regarding invoicing symptom-directed physical examinations that came up during preparation of the site contracts (**Modified sections:** Tables 2 and 12).
- Clarified that clinical plasmacytoma assessments are to be performed if clinically indicated at MM Disease Assessment Visits and at Durability of Response and Survival Follow-up Visits. Also corrected the window for detection of plasmacytomas at baseline by physical examination/palpation from "within 45 days" to "within 28 days" prior to C1D1 in footnote #21 of Table 2 (**Modified sections:** Section 11.3.1.8 and Tables 2 and 12).
- Clarified that a skeletal survey is required at the EoT Visit (**Modified section:** Table 2).

Study Treatment Administration

- Removed the requirement for dose escalation for patients in the SVd Arm who do not achieve at least a PR within the first 2 cycles, are tolerating SVd well, and do not have any AEs related to study treatment Grade >2 at the time of dose escalation. Dose escalation is no longer be required for these patients, however, a dose escalation may still be considered. This change was made to provide a greater margin of safety by making a determination for escalation of the selinexor dose based on the medical status of each individual patient. Also clarified that dose escalation is an option for all selinexor-containing regimens (**Modified sections:** Synopsis, Section 10.2.4.1, and Tables 8, 11, and 14; **New section**: Section 10.2.5).

Multiple Myeloma Disease Assessments

- Added a requirement for baseline bone marrow aspirate at Screening for all because the expectation in the field is that a baseline bone marrow aspirate is necessary to obtain accurate 17p status prior to starting a new therapy, Also, clarified that a portion of the bone marrow aspirate collected at Screening will be provided to the central laboratory for karyotyping and fluorescence in situ hybridization (FISH) analysis to confirm diagnosis and classify cytogenetic MM subtypes for R-ISS staging. (**Modified sections:** Section 11.3.1.9 and Table 2).
- Removed turbidometry as an acceptable method for measuring quantitative Ig levels because, unlike nephelometry, turbidometry cannot be used to assess response. Also clarified that nephelometry may be used in place of SPEP for routine M-protein measurement for patients with IgD myeloma in addition to patients with IgA myeloma (**Modified sections:** Sections 11.3.1 and 11.3.1.3).

PK Assessments

- Added PK assessments for bortezomib and selinexor in a subset of patients randomized to each arm (ie, the Vd Arm and the SVd Arm) in order to explore exposure-response relationships and drug-drug interactions between bortezomib and selinexor, and to evaluate any differences in PK related to age, race, sex, BMI, baseline disease state, or other demographic characteristics (**Modified sections:** Section 10.2.3.1 and Table 2; **New Sections** 5.1.4, 5.2.4, 11.4, and 13.6).

Clinical Safety Assessments

- Clarified that BSA should be recalculated if the patient's weight fluctuates substantially from baseline (ie, >20%) during treatment (including Vd, SVd, SVdX, and SdX) (**Modified sections:** Global).

Analysis Populations

- Revised the definition of the per-protocol (PP) population from all ITT patients who have received "any amount" to "at least 1 dose "of study treatment to clarify that the population does not include patients who have not received study treatment (**Modified sections:** Synopsis and Section 13.3.2).

Efficacy Analysis

- Added justification for the sample size calculation assumptions. This change was made to address the FDA request to provide justification for the assumptions for the sample size calculation (**Modified sections:** Sections 13.2.1 and 13.2.2).
- Specified that an independent third party (the DSMB) will conduct and review the sample size re-estimation and that an interim analysis charter will be created to outline the operational procedures associated with both PFS IAs. This change was made to address the FDA recommendation that the conduct/review of the sample size re-estimation be conducted by an independent third party (**Modified section:** Section 13.2.3.1).
- Clarified timing and details for the second IA (**Modified section:** Section 13.2.3.2).
- Added a sensitivity analysis using the Breslow-Day test to evaluate the homogeneity of odds ratios across the strata associated with the ORR endpoint and the two secondary efficacy endpoint analyses which are analyzed using the Cochran-Mantel-Haenszel test. This change was made to address the FDA request to include a sensitivity analysis to evaluate the robustness of secondary efficacy endpoints analysis results. (**Modified sections:** Sections 13.5.1 and 13.5.2).
- Added sensitivity analyses for the primary efficacy endpoint and the key secondary efficacy endpoints to address the FDA request to provide sensitivity analyses to evaluate the robustness of efficacy results in the protocol, which includes different censoring rules for the analyses of time-to-event endpoints. The sensitivity analyses, based on the guidance "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" will consider the events in which patients have taken other anticancer therapy, missed assessments, or been lost-to-follow-up (**Modified sections:** Sections 13.5.1.1, 13.5.1.2, and 13.5.2).

- Clarified that all changes in MM disease assessments will be based on baseline MM disease assessments from C1D1 of study treatment (**Modified sections:** Sections 5.2.1 and 13.5.1.2).
- Added a method for testing the proportional hazard assumption associated with the analyses of the primary and key secondary time-to-event endpoints. This change was made to address the FDA request to include a method for testing the assumption of the proportional hazard model and evaluate the impact of the varying hazard ratios on the conclusion (**Modified section:** Section 13.5.1.1).
- CCI

Safety Analysis

- Revised the correction for QTc from Bazett's to Fridericia's to address the FDA request to use the Fridericia's correction for QTc correction instead of Bazett's. Fridericia's is more effective for rejection of false positive results (Guidance for Industry entitled E14 Clinical Evaluation of QT/QTc Interval Prolongation) (**Modified sections:** Sections 11.5.1.3, 13.7.5, and 15).

Safety Definitions, Recording and Reporting

- Revised start time for recording of AEs from "from the first dose of study treatment on C1D1 "to "after the patient has provided informed consent" to ensure compliance with regulations (**Modified sections:** Section 12.1.2 and Table 2).
- Minor wording changes to improve clarity related to reporting of SAEs and pregnancies (**Modified sections**: Sections 12.2, 12.2.2, 12.2.3, and 12.3.1).
- Added the following regulatory definition for serious hospitalizations: "A hospitalization meeting the regulatory definition for 'serious' is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility." (**Modified section:** Section 12.2).
- Expanded section related to handling overdoses to cover, abuse, misuse, medication errors, and occupational exposure and created related subsections. Also removed the paragraph detailing supportive measures for patients who develop liver function test abnormalities in the event of an overdose and added detailed reporting requirements (**Modified section:** Section 12.3.2).
- Moved text related to supportive measures for possible hepatic GSH depletion in the case of extreme overdose to the supportive care section because it is not relevant to the safety section (**Modified section:** Section 12.3.2; **New section:** 10.3.5).