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

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]			

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.

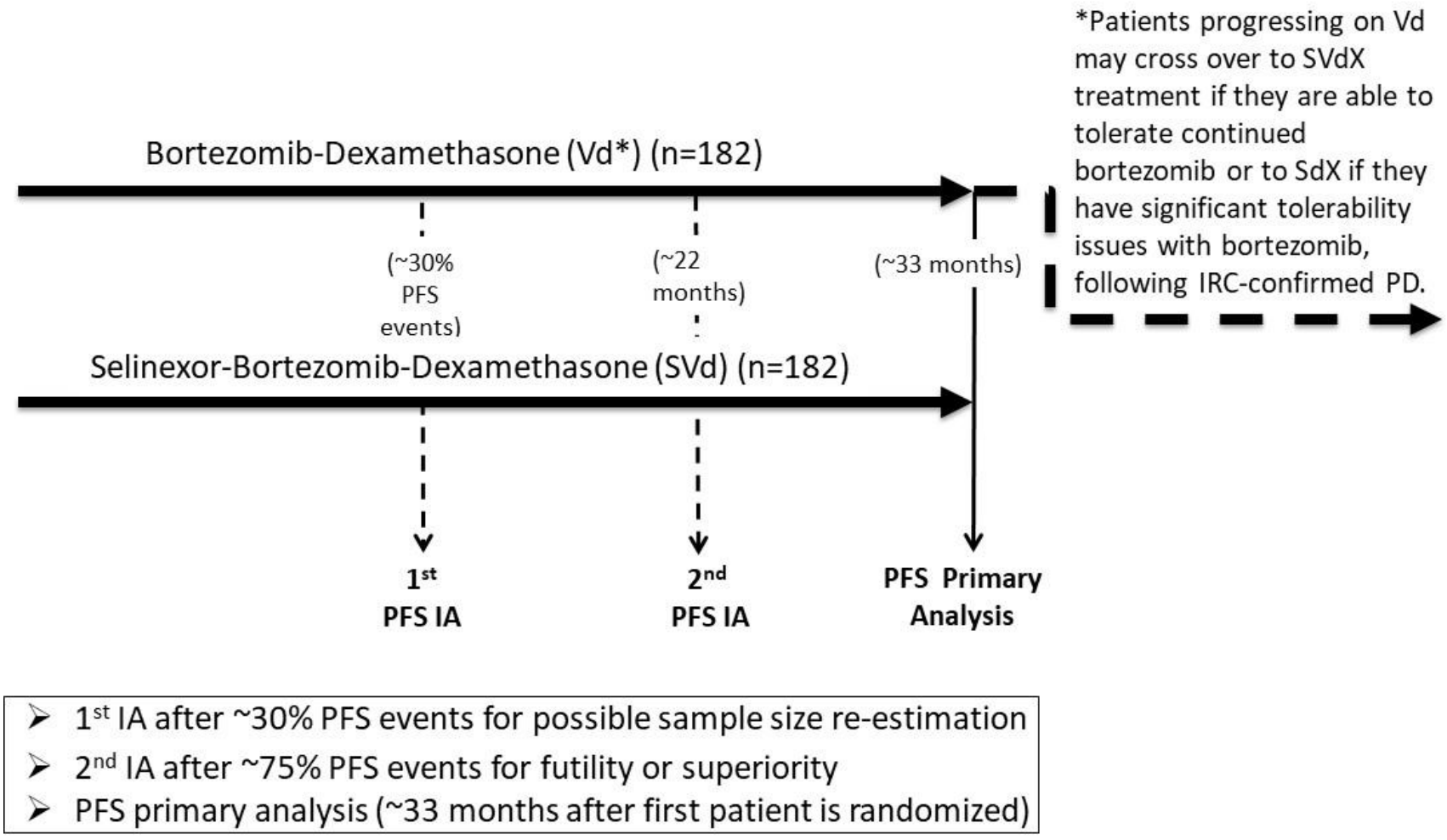
[a] If the patient's weight fluctuates substantially from baseline (ie, >20%) during treatment, BSA should be recalculated.

[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.

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.

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

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

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

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.

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).

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.

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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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.

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

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							

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

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.

- 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,

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.

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;

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.

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

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[redacted]

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.

13.7.2.7. 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.

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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.