STATISTICAL ANALYSIS PLAN

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)

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

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

The undersigned has developed this statistical analysis plan (SAP):

Name/Title	Signature	Date
PPD PhD PPD PPD	PPD	PPD

The undersigned have reviewed this SAP and approve it in its entirety:

Name/Title	Signature	Date
PPD MD PPD PPD PPD	PPD	PPD
PPD MD PPD PPD	PPD	PPD
PPD PPD PPD	PPD	PPD
PPD PhD PPD PPD	PPD	PPD

DOCUMENT HISTORY

Version	Date	Author(s)	Brief Summary of Changes
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2.0	September 30, 2019	PPD PPD	See Section 1.8 changes to Version 1.0
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	**Definition**
AE	adverse event
AECI	adverse event of clinical interest
ATC	anatomical therapeutic class
BIW	twice weekly
BSA	body surface area
C1D1	cycle 1 day 1
CI	confidence interval
CIPN20	chemotherapy-induced peripheral neuropathy
CMH	Cochran-Mantel-Haenszel
CMQ	Customized MedDRA Query
CP	conditional power
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CXDX (e.g., C1D1)	cycle X day X (e.g., cycle 1 day 1)
DBP	diastolic blood pressure
DOR	duration of response
ECG	electrocardiogram
ECOG	eastern cooperative oncology group
eCRF	electronic case report form
CCI	[redacted]
EORTC	European Organization for Research and Treatment of Cancer
EoT	End of Treatment
FLC	free light chain
hr	hour
HR	hazard ratio
HR-QoL	health-related quality of life
IA	interim analysis
ICH	International Council for Harmonisation

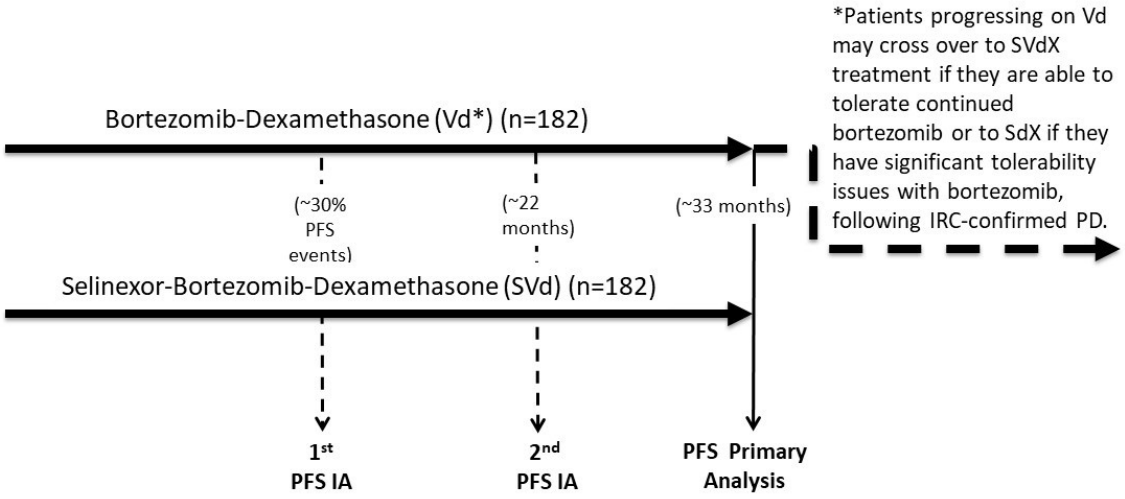
Abbreviation	Definition
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
IRC	Independent Review Committee
ISS	IMWG international staging system
ITT	intent-to-treat
KM	Kaplan-Meier
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MR	minimal response
MRD	minimal residual disease
NCI	National Cancer Institute
NE	not evaluable
ORR	overall response rate
OS	overall survival
PCS	potentially clinical significance
PD	progressive disease
PFS	progression-free survival
PI	proteasome inhibitor
PP	per-protocol
PR	partial response
PT	preferred term
CCI [redacted]	[redacted]
QoL	quality of life
QW	once weekly
R-ISS	Revised International Staging System
RRMM	relapsed or refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
sCR	stringent complete response

Abbreviation	Definition
SD	stable disease
SdX	selinexor plus low-dose dexamethasone treatment after crossover
SI	international system of units
SMQ	Standard MedDRA Query
SOC	system organ class
SSR	sample size re-estimation
SVd	selinexor plus bortezomib plus low-dose dexamethasone
SVdX	SVd treatment after crossover
TEAE	treatment-emergent adverse event
TTNT	time-to-next-treatment
TTR	time to response
ULN	upper limit of normal
VAS	visual analogue scale
Vd	bortezomib plus low-dose dexamethasone
VGPR	very good partial response
WHO	world health organization

1. OVERVIEW AND INVESTIGATIONAL PLAN

1.1. STUDY DESIGN

KCP-330-023 is a phase 3, 2-arm, randomized, active comparator-controlled, open-label, multicenter study that compares the efficacy and health-related quality of life (HR-QoL) and assesses 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 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.

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 will be stratified based on:

- 4 Regions
  - Region 1 (USA, Canada)
  - Region 2 (Austria, Belgium, France, Germany, Italy, Spain, UK, Israel, Australia)
  - Region 3 (Czech Republic, Greece, Hungary, Poland)

  - Region 4 (India, Russia, Ukraine, Bulgaria, Romania, Serbia)
- 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 et al., 2015). If data for chromosomal abnormalities 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 progressive disease (PD) that is confirmed by the Independent Review Committee (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. Patients who cross over will be referred to as SVdX patients or SdX patients, respectively.

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

The Schedule of Assessments is provided in Section 7.1. Patients randomized to the SVd and Vd Arms will undergo MM evaluations every 3 weeks from baseline MM evaluations on cycle 1 day 1 (C1D1) (regardless of dose interruptions) through the first day of Week 37 (i.e., 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. SVdX/SdX patients will undergo MM evaluations every 5 weeks. Dose modifications for selinexor to manage tolerability will be allowed.

Study treatment (SVd, Vd, SVdX, or SdX) may continue until PD is confirmed by the IRC or the investigator according to the International Myeloma Working Group (IMWG) criteria or patient decision to discontinue study treatment, pregnancy, unacceptable adverse events (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.

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 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 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.

1.2. OBJECTIVES

1.2.1. Primary Objective

- 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

1.2.2. Secondary Objectives

- 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 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

1.2.3. Exploratory Objectives

CCI

[redacted]

1.3. ENDPOINTS

1.3.1. Primary Endpoint

- PFS, defined as time from date of randomization until the first date of IRC-confirmed PD, per IMWG response criteria, or death due to any cause, whichever occurs first.

1.3.2. Secondary Efficacy Endpoints

1.3.2.1. Key secondary Efficacy Endpoints

- ORR, defined as any response ≥ PR (i.e., 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)

1.3.2.2. Non-Key secondary Efficacy Endpoints

- OS, defined as time to death, measured from the date of randomization until death due to any cause
- DOR, defined as the duration from first 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 from date of first dose of SVdX treatment after crossover from the Vd Arm until the first date of PD, or death due to any cause

- TTNT, defined as duration from date of randomization to start of next anti-MM treatment or death, whichever occurs first
- TTR, defined as duration from date of randomization until the date of first IRC-confirmed response (≥ PR) per IMWG response criteria
- PFS2 (PFS for patients who receive post-SVd/Vd/SVdX treatment), defined as the duration 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

1.3.3. Secondary Safety Endpoints

1.3.3.1. Key secondary Safety Endpoints

- 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

1.3.3.2. 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

1.3.4. Secondary HR-QoL Endpoint

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

1.3.5. Exploratory Endpoints

CCI [redacted]

1.4. DETERMINATION OF SAMPLE SIZE

CCI [redacted]

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[redacted]

1.5. STUDY PLAN

For each patient that signs the informed consent, the study consists of:

- Screening/baseline visit: occurs within 28 days prior to receiving the 1st dose of study treatment
- Treatment period: there is no maximum treatment duration. Patients will be treated until PD is confirmed by the IRC or the investigator according to the IMWG criteria 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
- Follow-up period: up to 5 years after their last dose of SVd/Vd/SVdX/SdX treatment, patients will be contacted approximately every 3 months for durability of response and survival follow-up

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.

Please refer Table 7-1 to for detailed schedule of assessment and study activities.

1.6. INTERIM ANALYSIS

1.6.1. Interim Analysis for Sample Size Re-estimation

The first interim analysis (IA) was conducted with data cut of 21 Jan 2019 after 113 events were accrued. The purpose of the first IA was for sample size re-adjustment. The DSMB met on 21 Feb 2019 and based on the safety and efficacy data, the DSMB recommendation was continuation of the study with no change to safety monitoring and no sample size adjustment. Thus, there is no need for type I error adjustment for final analysis according to CHW method (Cui et al., 1999).

1.6.2. Interim Analysis for Futility or Superiority

A second interim analysis was originally planned after approximately 75% of the planned number of PFS events (i.e., approximately 201 PFS events) have occurred, and would allow for a conclusion of efficacy, and stopping for futility (non-binding).

Due to concerns that the trial is not going to reach the planned 267 events, and that it would take an extended period of time to accrue additional PFS events with minimal gain in power, the Sponsor believes that it is in the best interest of patients to use the second IA as the final efficacy analyses no matter the outcome is positive or not. With DSMB agreement, the Sponsor is revising analysis plan to use the second IA as the final PFS analysis and use all one-sided alpha of 0.025.

1.7. MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

Changes to Protocol v4.0

The final PFS analysis will be conducted when the second IA was originally planned (i.e. after 201 PFS events were occurred) and the final analysis will use all one-sided alpha of 0.025. The null hypothesis of PFS endpoint will not be re-tested at any subsequent timepoint.

1.8. STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Changes to Version 1.0

Changes throughout the document include minor editorial changes.

Section 2.3

- Clarified the start date of the SVdX (SdX) treatment to be the earliest non-zero dose date of at least 1 dose of selinexor or bortezomib (for SVdX treatment only) or dexamethasone for SVdX (SdX) treatment after crossover.

Section 2.2.2, 2.3, 3.3.1, 5.1.1

- Clarified that for patients who cross over from the Vd Arm to the SVdX or SdX treatment, the following derivations will be based on the initiation of the SVdX and SdX treatment:
    - the handling of missing or partial dates for AE or concomitant medications
    - definition of concomitant medications
    - the end date of Vd treatment
    - TEAE definition after crossover to SVdX/SdX treatment

Section 3.1.1

- Clarified the Per-protocol (PP) population definition.

Section 3.2.2.1

- Clarified that best response and duration of most recent prior anti-MM regimen will be summarized.
- Modified the calculation of the duration of most recent prior anti-MM regimen in days.

Section 4.1.1, 4.2.1.1, 4.2.2.1, 4.2.2.3, 4.2.2.6, 4.2.2.7, 4.2.2.9, 4.3.3 and 5.3

- Removed region as the stratum used for analyses and clarified that the stratification factors include prior PI therapies, number of prior anti-MM regimens, and R-ISS stage at study entry.

Section 4.2.2.1, 4.2.2.5, 4.2.2.6, 4.2.2.7, 4.2.2.8, and 4.3.3

- Clarified the censoring criteria for patients who do not have an event in the corresponding sections.

Section 5.1.1, 5.1.5

- Modified "Adverse Event of Special Interest (AESI)" to "Adverse Event of Clinical Interest (AECI)".
- Modified the AECI categories.

Changes to Version 2.0

Changes throughout the document include minor editorial changes.

Section 1.6.1

- Provided the results of the first IA.

Section 1.6.2 and 1.7

- Changed timing of the final PFS analysis to when the second IA was originally planned (i.e. after 201 PFS events were occurred).

Section 4

- Removed CHW method since sample size did not change after the first IA.

Section 4.4

- Removed the type I error adjustment for the second IA since the second IA will be treated as final analysis.

Section 5.1.1

- Add more details to the definition of TEAE.

Section 5.1.5

- Modified the AECI categories.

2. GENERAL STATISTICAL METHODS AND DATA HANDLING

This statistical analysis plan (SAP) outlines the methods to be used in the analysis of clinical data in order to answer the study objectives. Populations for analysis, data handling rules, and statistical methods are provided. This SAP does not include endpoints and methods to be used in the analysis of PK data; these will be included in a separate plan.

2.1. GENERAL ANALYSIS METHODS

This is a 2-arm, randomized, open-label study. All summary statistics will be computed and displayed among the corresponding analysis population, and by each scheduled assessment time point whenever applicable. Summary statistics for continuous variables will minimally include n, median, mean, standard deviation, minimum, and maximum. For categorical variables, frequencies and percentages will be presented with the denominators for the percentages determined based on the analysis population used, unless otherwise specified. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries. Graphical displays may be provided as appropriate.

2.2. MISSING DATA HANDLING IN DATA PRESENTATION

In general, missing baselines will not be imputed. The following approaches are default methods for missing data handling in summary tables.

- Categorical data at baseline will be summarized using counts (n) and percentages (%). Denominator will be the total number of people in a corresponding treatment arm, based on the population specified for the summary, unless otherwise specified. Missing data may be presented as a separate category.
- Continuous data will be summarized based on observed data only.

2.2.1. Handling of Computation of Treatment Duration if Study Treatment End of Treatment Date is Missing

For the calculation of treatment duration, the date of the last dose of study treatment is equal to the date of last study treatment dosing reported on study treatment dosing form. If all the dosing dates are missing, then the duration is missing.

The last dose intake should be clearly identified on the eCRF dosing page and should not be approximated by the last returned package date.

2.2.2. Handling of Missing/partial Dates for Adverse Events or Concomitant Medications

In general, the imputation should be conservative such that onset dates should be imputed to be as early as possible and resolution dates will be imputed to be as late as possible. Impute resolution date first and then impute onset date using imputed resolution date. However, for categorization purpose, if the partial AE onset date information does not indicate whether the AE started prior to treatment or after the treatment-emergent adverse event (TEAE) period, the AE will be classified as treatment-emergent. Handling of missing or partial dates for AE or concomitant medications will consider the start date of SVdX or SdX treatment for patients who cross over from the Vd Arm to the SVdX or SdX treatment.

These data imputations are for categorization purpose or calculation of AE duration, and will not be used in listings.

Refer to the Karyopharm Biostatistics and Statistical Programming Rule Book for details on imputation methods.

2.2.3. Handling of Missing or Partial Birth Date for Calculation of Age

Refer to the Karyopharm Biostatistics and Statistical Programming Rule Book for details on imputation methods.

2.2.4. Handling of Missing Assessment of Relationship of AEs to Study Treatment

If the assessment of the relationship to study treatment is missing, then the relationship to study treatment in the frequency tables is considered as related.

2.2.5. Handling of Missing Data in Patient-Reported QoL Measurements

For patient-reported QoL measurements, missing data will be handled as described in the CCI EORTC-QLQ-CIPN20, CCI scoring manuals.

2.3. STUDY TREATMENT DOSING DATE

Study treatment dosing date is the date on which a patient actually received study treatment (partial or complete), as recorded on the study drug exposure eCRF.

The start date of study treatment is identified as follows:

- SVd treatment: Earliest non-zero dose date of at least 1 dose of selinexor, bortezomib or dexamethasone
- Vd treatment: Earliest non-zero dose date of at least 1 dose of bortezomib or dexamethasone
- SVdX treatment: Earliest non-zero dose date of at least 1 dose of selinexor, bortezomib or dexamethasone for SVdX treatment after crossover
- SdX treatment: Earliest non-zero dose date of at least 1 dose of selinexor or dexamethasone for SdX treatment after crossover

For patients who cross over from the Vd Arm to the SVdX or SdX treatment, there will be two start dates of study treatment before and after the crossover.

The end date of study treatment is identified as follows:

- SVd treatment: Latest non-zero dose date of selinexor, bortezomib or dexamethasone.
- Vd treatment:
  - For patients who cross over to the SdX treatment or SVdX treatment, the date of last study treatment is the latest non-zero dose date of bortezomib or dexamethasone before the first dose of the SVdX or SdX treatment.
  - For patients who do not cross over to the SdX treatment or SVdX treatment, the date of last study treatment is the latest non-zero dose date of bortezomib or dexamethasone.

- SVdX treatment: Latest non-zero dose date of selinexor, bortezomib or dexamethasone after crossover
- SdX treatment: Latest non-zero dose date of selinexor or dexamethasone after crossover

For patients who cross over from the Vd Arm to the SVdX or SdX treatment, there will be two end dates of study treatment before and after the crossover.

2.4. OBSERVATION PERIOD

For the patients who are in the SVd or Vd Arm, excluding those who cross over from the Vd Arm to the SVdX or SdX treatment, the observation period will be divided by the following:

- SVd Arm:
  - The pre-treatment period is defined as the time from the signed informed consent date up to the time before the start date of SVd treatment.
  - The treatment period is defined as the time from the start date of SVd treatment up to the end date of SVd treatment + 30 days inclusive.
  - The post-treatment period is defined as the time beyond the treatment period.
- Vd Arm:
  - The pre-treatment period is defined as the time from the signed informed consent date up to the time before the start date of Vd treatment.
  - The treatment period is defined as the time from the start date of Vd treatment up to the end date of Vd treatment + 30 days inclusive.
  - The post-treatment period is defined as the time beyond the treatment period.

For the patients who cross over from the Vd Arm to the SVdX or SdX treatment, the observation period will be divided by the following:

- Vd Arm (before crossover):
  - The pre-treatment period is defined as the time from the signed informed consent date up to the time before the start date of Vd treatment.
  - The treatment period is defined as the time from the start date of Vd treatment to the end date of Vd treatment + 30 days inclusive, or the start date of SVdX or SdX treatment exclusive, whichever occurs first.
- After crossover to the SVdX treatment:
  - The pre-treatment period is defined as the time from after the end date of Vd treatment period up to the start date of SVdX treatment exclusive.
  - The treatment period is defined as the time from the start date of SVdX treatment to the end date of SVdX treatment + 30 days inclusive.
  - The post-treatment period is defined as the time beyond the treatment period of SVdX treatment.
- After crossover to the SdX treatment:

- The pre-treatment period is defined as the time from after the end date of Vd treatment period up to the start date of SdX treatment exclusive.
- The treatment period is defined as the time from the start date of SdX treatment to the end date of SdX treatment + 30 days inclusive.
- The post-treatment period is defined as the time beyond the treatment period of SdX treatment.

Please refer to Section 2.3 for the definition of start and end date of study treatment.

2.5. STUDY DAY CALCULATION

Study Day 1 is the date of first study treatment, which is the start date of SVd treatment or Vd treatment for patients in the SVd Arm or Vd Arm respectively. The day before Day 1 is considered Day -1; there is no Day 0.

The study day after the crossover for patients who cross over from the Vd Arm to the SVdX or SdX treatment will also be calculated using the start date of study treatment after crossover as reference point. For example, the first dose date of SVdX or SdX treatment will be referred as Crossover Day 1 or Day 1X.

A patient is considered as treated in a cycle if the patient received any non-zero dose of either selinexor or bortezomib or dexamethasone in that cycle.

Study day for a given assessment is defined as

- the assessment date – the date of first study treatment + 1 if the assessment date is on or after Day 1, or
- the assessment date – the date of first study treatment if the assessment date is before Day 1.

2.6. BASELINE MEASUREMENT

For patients in the SVd or Vd arm, excluding those who cross over from the Vd Arm to the SVdX or SdX treatment, the baseline value is defined as the latest value prior to the start date of study treatment.

For patients who cross over from the Vd Arm to the SVdX or SdX treatment, baseline values will be based on the following:

- Before crossover: Baseline value is defined as the latest value prior to the first dose of Vd treatment.
- After crossover: Baseline value is defined as the latest value prior to the first dose of SVdX or SdX treatment.

In the case an assessment performed on the same date as the first dose, but it is impossible to determine the evaluation time relative to the time of taking the first dose, the evaluation time will be assumed to be following the protocol-defined schedule.

2.7. VISIT WINDOWS

For safety data that are summarized/plotted by time points, non-missing assessments from all scheduled and unscheduled visits will be mapped to an appropriate analysis visit using a windowing scheme. Analysis visit windows are defined in Table 2-1 to Table 2-2. If there are 2 or more assessments mapped to the same analysis visit for a patient, the assessment that is closest to the target visit day will be used for analysis. If there are 2 or more assessments mapped to the same analysis visit with the same distance from the target visit day, then select the latest one for the analysis.

Table 2-1 Visit Windows for Clinical Laboratory Tests and Vital Signs for patients in the SVd or Vd Arm

Analysis Visit Name	Target Visit Day	Study Day Range in Window
Baseline	Day 1	Prior to or on Day 1
Day 8	Day 8	Day 2 to 15
Day 22	Day 22	Day 16 to 32
Day 43	Day 43	Day 33 to 53
Day 64	Day 64	Day 54 to 74
Day 85	Day 85	Day 75 to 95
Day 106	Day 106	Day 96 to 116
…		
(every 21 days through Day 253)		
Day 253	Day 253	Day 243 to 263
Day 288	Day 288	Day 264 to 305
Day 323	Day 323	Day 306 to 340
…		
(every 35 days)		
NOTE: Day 1 is the date of first selinexor or bortezomib or dexamethasone dose. The visit window is +/- 10 days for post-baseline visits through the first day of Week 37 (i.e. Day 253), except for Day 8 and Day 22 visit. After the first day of Week 37, the visit window is +/- 17 days except for Day 288. Analysis visit and visit window may change for certain parameters depending on the data availability.		

Table 2-2 Visit Windows for Clinical Laboratory Tests and Vital Signs for patients who cross over from the Vd Arm to the SVdX or SdX treatment

Analysis Visit Name	Target Visit Day	Study Day Range in Window
Crossover Baseline	Crossover Day 1	Prior to or on Crossover Day 1
Crossover Day 36	Crossover Day 36	Crossover Day 2 to 53
Crossover Day 71	Crossover Day 71	Crossover Day 54 to 88
Crossover Day 106	Crossover Day 106	Crossover Day 89 to 123
…		
(every 35 days)		
NOTE: Crossover Day 1 is the date of first selinexor dose after crossover. The visit window is +/- 17 days for post-baseline visits, except for the Crossover Day 36 visit. Analysis visit and visit window may change for certain parameters depending on the data availability.		

2.8. SUBGROUPS

To determine whether the treatment effect is consistent across various subgroups. Subgroup analyses on the primary endpoints (PFS and ORR) and DOR will be performed using the following subgroups:

- Age group (<65 versus ≥65)
- Sex (male versus female)
- Race (white versus others)
- Ethnicity (Hispanic or Latino versus Not Hispanic or Latino)
- Region (region 1, region 2, region 3 and region 4 as defined in randomization)
- Prior PI therapies (Yes or No)
- Patients with 1 prior anti-MM regimen versus >1 prior anti-MM regimen
- Baseline R-ISS (Stage III versus Stage I or II)
- Baseline ISS (Stage III versus Stage I or II)
- Baseline single cytogenetic alterations (del[17p]; translocation t[4;14]; translocation t[14;16]; 1q21 amplification) for high risk population and separately for each CA
- Last PI received prior to the 6-month PI treatment-free interval for those patients who received prior PI (bortezomib, carfilzomib, ixazomib, other)

2.9. POOLING OF CENTERS FOR STATISTICAL ANALYSES

All participating centers in the study will be pooled together for analyses.

2.10. COMPUTING AND CODING STANDARDS

Activities will be performed using the following tools:

Table, listing, and figure production	SAS Version 9.4 or higher
Coding	
AEs	MedDRA Version 20.1
Medical Histories	MedDRA Version 20.1
Prior and Concomitant Medications	WHO DDE Version September 2017 B3
Grading	
AEs	CTCAE Version 4.03
Labs	CTCAE Version 4.03

3. PATIENT INFORMATION

3.1. DISPOSITION OF PATIENTS AND ANALYSIS POPULATIONS

Patient disposition will be summarized in each of the following categories:

- Screened patients, defined as any patient who has signed the informed consent form
- Screen failure patients, defined as any patient who signs the informed consent form but who is not randomized into the study
- Patients who were randomized
- Patients who were randomized but did not receive any dose of study treatment (partial or complete)
- Patients who received at least one dose of study treatment (partial or complete)
- End of treatment:
    - Patients who discontinued treatment and primary reason for treatment discontinuation
- Survival follow-up status
    - Patients in survival follow-up
    - Patients who have completed 5-year survival follow-up
    - Patients who died during survival follow-up
    - Patients who discontinued from the study without completing 5-year survival follow-up
- End of study:
    - Patients who withdrew from study and primary reason for study withdrawal

The number of patients in each analysis population and the number of patients who cross over from the Vd Arm to the SVdX or SdX treatment will be presented.

A separate summary of disposition of patients who cross over from the Vd Arm to the SVdX or SdX treatment will be provided.

A by-patient listing of study completion information, including the reason for study withdrawal may also be provided.

3.1.1. Efficacy Populations

Intent-to-Treat (ITT) Population

The ITT population will consist of all patients who are randomized to study treatment, regardless of whether or not they receive study treatment. This population will be used for primary analyses of efficacy. Patients will be analyzed in the treatment arm to which they were randomized and strata assignment at the time of randomization.

Per-protocol (PP) Population

The per-protocol (PP) population will consist of all ITT patients who have study treatment compliance ≥ 70% (see Section 4.2 for the definition of study treatment compliance) 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.

3.1.2. Safety Population

The Safety population will consist of all patients who have received at least 1 dose of study treatment. Patients will be analyzed according to the treatment they received.

3.1.3. Additional Analysis Populations

Analysis of selected efficacy and safety endpoints will be conducted in the following populations respectively:

SVdX (Crossover from Vd) Population

The SVdX population will consist 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 and have received at least 1 dose of selinexor.

SdX (Crossover from Vd) Population

The SdX population will consist 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 and have received at least 1 dose of selinexor. 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 (e.g., due to Grade > 2 peripheral neuropathy or Grade ≥ 2 peripheral neuropathy with pain).

3.2. DEMOGRAPHICS, MEDICAL HISTORY AND BASELINE CHARACTERISTICS

In general, the baseline value is defined as latest value prior to the first dose of study treatment. Demographics, medical history and baseline characteristics will generally be summarized among ITT and safety populations, unless otherwise specified. P-values on demographic, medical history and baseline characteristic data will not be calculated.

3.2.1. Demographic Data

Demographic characteristics will be summarized by treatment arm and overall, and will include sex (female, male), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other), ethnicity, and age at study entry.

The summary of demographic data will be also provided for patients who cross over from the Vd Arm to the SVdX or SdX treatment.

3.2.2. Prior Antineoplastic Therapy

The summary of prior antineoplastic therapy will be presented.

3.2.2.1. Antineoplastic Medication

Prior antineoplastic medication will be summarized for the ITT population with the following variables:

- Number of patients who received any prior antineoplastic medication for MM
- Number of patients who received any prior antineoplastic medication for other malignancy
- Number of unique prior anti-MM medication
- Number of prior anti-MM regimen (summarized as a continuous variable and as a categorical variable, with cutoff of 1, 2, 3, >3 prior anti-MM regimen)
- Best response to most recent prior anti-MM regimen
- Days from end date of most recent prior anti-MM regimen to start of study treatment will be calculated as date of randomization – stop date of most recent prior anti-MM medication +1
- Duration of most recent prior anti-MM regimen (weeks)
- Exposure/refractory status to each individual MM treatment including lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, alkylating agent, glucocorticoid, anthracyclines, and stem cell transplants

The detailed history of prior antineoplastic medication including start and end dates of the medication, best response, whether patient progressed or relapsed during or after treatment, discontinuation due to intolerability or toxicity may also be provided in a data listing.

3.2.2.2. Prior Radiotherapy

The following variables of prior radiotherapy will be summarized using ITT population:

- Number of patients who received any prior radiotherapy for MM
- Number of patients who received any prior radiotherapy for other malignancy
- Number of prior anti-MM radiotherapy (summarized as a continuous variable and as a categorical variable, with cutoff of 1 and >1 prior radiotherapy)
- Days from most recent prior anti-MM radiotherapy to start of study treatment
- Best response to most recent anti-MM radiotherapy

Prior radiotherapy may also be provided in a data listing.

3.2.2.3. Prior Antineoplastic Surgery

The following variables of prior antineoplastic surgery will be summarized using ITT population:

- Number of patients who received any prior antineoplastic surgery for MM
- Number of patients who received any prior antineoplastic surgery for other malignancy

- Procedure of prior anti-MM surgery
- Type of resection of prior anti-MM surgery

Prior antineoplastic surgery may also be provided in a data listing.

3.2.3. Medical History - Conditions and Procedures

Medical history other than MM will be summarized in the ITT population by system organ class (SOC) and preferred term (PT) using the number and percentage of patients who have at least one occurrence of a SOC and PT. The summary will be sorted by alphabetic order in SOC, and further by decreasing frequency of PT within each SOC. When more than one PT has the same frequency, the order of presentation will be alphabetical in PTs.

Medical history information may also be provided in a data listing.

3.2.4. Disease History

Summary statistics including the number and percentage of patients will be presented for the following variables:

- Disease stage at initial diagnosis
- Disease stage at diagnosis of active (symptomatic) myeloma
- Current disease stage at screening according to ISS and R-ISS for MM
- Smoking history including status (Never used, Current, Former) and frequency

For the following variables, results at initial diagnosis will be summarized:

- β2 microglobulin
- Albumin
- LDH
- Immunoglobulin type
- Light chain type
- Availability of bone marrow results
- % plasma cells

Chromosomal abnormality at initial diagnosis will be presented in a separate table from above:

- Availability of FISH results
- Number of patients with High-Risk Chromosomal Abnormalities (i.e. patients with any of del[17p]/p53, t[14;16], t[4; 14], or 1q21)
- Number of patients with del(17p)/p53
- Number of patients with t(14;16)
- Number of patients with t(4;14)
- Number of patients with 1q21 amplification

- Number of patients with del (13)
- Number of patients with t(6;14)
- Number of patients with t(11;14)
- Number of patients with t(14;20)

3.2.5. Baseline Characteristics

Summary statistics including the number and percentage of patients will be presented for the following variables:

- Baseline height (cm)/ weight (kg)/ body surface area (m2)/ BMI (kg/m2)
- Baseline ECOG performance status
- Duration from initial diagnosis (years)
- Baseline creatinine clearance (summarized as a continuous variable and as a categorical variable, with cutoff of < 30, 30 to < 60 and ≥ 60)
- Number of unique ongoing medical history (Preferred Terms) per patient
- Number of unique ongoing medications (Anatomical Therapeutic Class [ATC] Level 4 and standard name) per patient

Serum immunofixation and urine immunofixation information at baseline including the following will be presented in a separate table from the above:

- M-component Ig type of the active myeloma for serum immunofixation
- M-component light chain type of the active myeloma for serum immunofixation
- M-component light chain type of the active myeloma for urine immunofixation

3.3. PRIOR AND CONCOMITANT MEDICATIONS AND PROCEDURES

Concomitant medication consists of any prescription or over-the-counter preparation, including vitamins, dietary supplements, over-the-counter medications, and oral herbal preparations taken during the study, as well as changes in medication. Patients may continue their baseline medication(s). Concomitant medications include any medications used to treat symptoms, concomitant diseases such as diabetes, hypertension, etc., AEs and intercurrent illnesses that are medically necessary as part of standard care. All concomitant medication(s) must be reported on the eCRF. Any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s), and any clinical findings, if applicable. Concomitant medication will generally be summarized among ITT and safety populations, unless otherwise specified.

All medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO DDE).

3.3.1. Prior and Concomitant Medications and Procedures

Prior medications are any treatments received by the patient prior to the first dose of study treatment. Prior medications can be discontinued before first dose of study treatment or can be ongoing during treatment period.

Concomitant medications are defined by the following for patients who are in the SVd or Vd arm, excluding those who cross over from the Vd Arm to the SVdX or SdX treatment:

- SVd Arm:
  Any treatments received by the patient concomitantly with study treatment (i.e. selinexor and/ or bortezomib and/or dexamethasone), from first dose of study treatment to last dose of study treatment + 30 days.
- Vd Arm:
  Any treatments received by the patient concomitantly with study treatment (i.e. bortezomib and/or dexamethasone), from first dose of study treatment to last dose of study treatment + 30 days.

Concomitant medications are defined by the following for patients who cross over from the Vd Arm to the SVdX or SdX treatment:

- Vd Arm (before crossover):
  Any treatments received by the patient concomitantly with study treatment (i.e. bortezomib and/or dexamethasone), from first dose of study treatment to the time before the first dose of SVdX or SdX treatment.
- After crossover to the SVdX treatment:
  Any treatments received by the patient concomitantly with SVdX treatment, from the first dose of the SVdX treatment to the last dose of study treatment + 30 days.
- After crossover to the SdX treatment:
  Any treatments received by the patient concomitantly with SdX treatment, from the first dose of the SdX treatment to the last dose of study treatment + 30 days.

Concomitant medications will be summarized according to the WHO DDE by the ATC level 2 (therapeutic level), level 4 (generic level) and standard name. A patient taking the same drug multiple times will only be counted once.

Note that a medication can be classified as both a prior medication and a concomitant medication.

The summary table of concomitant medications will be repeated for patients who cross over from the Vd Arm to the SVdX or SdX treatment.

The use of prior and concomitant medications and procedures may also be provided in a data listing.

Please refer to Section 2.2.2 for details on data handling rules related to computation, dates, imputation for missing dates.

3.4. EXTENT OF STUDY TREATMENT EXPOSURE AND COMPLIANCE

Study treatment is considered taken when patient actually receive any study drug (selinexor and/or bortezomib and/or dexamethasone, partial or complete). Extent of exposure and compliance will generally be summarized among ITT and safety populations, unless otherwise specified.

3.4.1. Extent of Study Treatment Exposure

The extent of exposure for the study treatment will be assessed using the following variables:

- Duration of study treatment exposure (summarized as a continuous variable and as a categorical variable)
- Number and percentage of patients with selinexor dose escalation
- Number and percentage of patients with dexamethasone dose escalation

The following will be presented separately for selinexor, bortezomib and dexamethasone:

- Duration of exposure (summarized as a continuous variable and as a categorical variable)
- Total dose received (summarized as a continuous variable)
- Average dose received per week (summarized as a continuous variable)
- Number and percentage of patients with dose reduction
- Number and percentage of patients with dose interruption
- Number and percentage of patients with missed dose

Duration of study treatment exposure is defined as the date of last study treatment - date of first study treatment + 1.

Average dose received per week is defined as total dose received divided by duration of exposure, presented in mg/week.

The summary of drug exposure information will be repeated for patients who cross over from the Vd Arm to the SVdX or SdX treatment.

Dosing information for each patient may also be provided in a data listing.

3.4.2. Compliance

Study treatment compliance will be summarized descriptively as a quantitative variable, calculated as

$$\frac{\text{number of actual study treatment doses taken}}{\text{number of study treatment doses scheduled}} \times 100.$$

A study treatment dose is considered scheduled if selinexor and/or bortezomib and/or dexamethasone is scheduled. The number and percentage of patients with study treatment compliance ≥70% will be provided. Note that the number of scheduled study treatment doses

does not include doses missed due to treatment interruption or other reasons not related to patient choice. Patients with study treatment compliance < 70% will be excluded from the PP population.

Selinexor compliance is defined similarly among the ITT and safety population as

$$\frac{\text{number of actual selinexor doses taken}}{\text{number of selinexor doses scheduled}} \times 100.$$

The number and percentage of patients with selinexor compliance ≥70% will be provided. Similarly, the number of scheduled selinexor doses does not include doses missed due to treatment interruption or other reasons not related to patient choice.

Bortezomib compliance is defined similarly among the ITT and safety population as

$$\frac{\text{number of actual bortezomib doses taken}}{\text{number of bortezomib doses scheduled}} \times 100.$$

The number and percentage of patients with bortezomib compliance ≥70% will be provided. Similarly, the number of scheduled bortezomib doses does not include doses missed due to treatment interruption or other reasons not related to patient choice.

4. EFFICACY

Patient response will be assessed centrally by an IRC according to IMWG response criteria (Kumar, 2016) for MM. Unless otherwise specified, MM response assessment refers to assessment determined by IRC.

The primary efficacy analyses will be conducted using the ITT population, unless otherwise specified. Efficacy analyses using the PP population will be considered as supportive.

For patients in the Vd arm, crossing over to SVdX or SdX will be considered as initiating a new MM treatment.

4.1. PRIMARY EFFICACY ENDPOINTS

4.1.1. PFS

Progression-free survival (PFS), defined as time from date of randomization until the first date of IRC-confirmed PD, per IMWG response criteria (Kumar, 2016), or death due to any cause, whichever occurs first. PD for the primary PFS endpoint will be assessed centrally by the IRC. If PD is based on 2 independent samples on an applicable disease parameter, the date of PD refers to the earlier date of the 2 independent samples.

The primary analysis of PFS will be performed by treatment (SVd versus Vd) on the ITT population. The analysis will be repeated for the PP population as a supportive analysis.

Duration is calculated as end date – start date +1. For instance, if a PFS event occurs, then PFS time (in days) is defined as event date – date of randomization +1. If a censoring event occurs, then PFS time is defined as the censoring date – date of randomization +1.

Please refer to Table 4-1 for details on PFS outcome status (PFS event vs. censored) and censoring definitions.

Table 4-1 PFS outcome and censoring definition

Situation	Date of event or censoring	Outcome
No adequate post-baseline disease status assessment unless death occurs prior to first post-baseline assessment	Randomization	Censored
Death before IRC-determined PD	Date of death	PFS event
IRC-determined PD	Date of PD	PFS event
No IRC-determined PD or death on or before a. database cut, b. withdrawal of informed consent, c. lost to follow-up,	Date of last adequate disease assessment on or prior to the earliest occurrence of the events (a. – e.) listed in the left column	Censored

d. documented treatment discontinuation e. start of new MM treatment, whichever occurs first		

The number and percentage of patients who had a PFS event will be reported. Median PFS with 95% confidence interval (CI) will be summarized using Kaplan-Meier (KM) method for each treatment arm. The KM curve for PFS will be provided by treatment arm.

A stratified log-rank test will be used to compare the PFS between treatment arms (SVd versus Vd) for the primary efficacy assessment. The strata will include prior PI therapies, number of prior anti-MM regimens, and R-ISS stage at study entry.

Hazard ratios and its 95% CI will be estimated by a stratified Cox proportional hazards model, with Efron's method of tie handling, with treatment as the factor. The strata will include prior PI therapies, number of prior anti-MM regimens, and R-ISS stage at study entry. 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:

- Events are defined as IRC-confirmed progression or death, whichever occurs first. Patients are censored at the date of last disease assessment if no progression is confirmed by the IRC, or treatment is discontinued for any reason, or new anticancer treatment is started, or death or progression occurs after 2 or more missed visits
- Similar to the primary PFS endpoint analysis but where treatment discontinuation for any reason is counted as an event
- Similar to the primary PFS endpoint analysis but where the initiation of non-study antineoplastic therapy is counted as an event
- 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.
- 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

4.2. SECONDARY ENDPOINTS

4.2.1. Analyses of Key Secondary Endpoints

The following 3 endpoints are defined as key secondary endpoints: ORR, the incidence of any ≥ Grade 2 peripheral neuropathy events and response rate for responses ≥VGPR will be tested at the time of the second PFS IA.

Statistical significance of key secondary endpoints will not be claimed until the primary endpoint of PFS have reached significance. The key secondary endpoints will be tested using the hierarchical testing procedure to maintain the overall type I error at a 1-sided 0.025 level of significance. More details on the strategy to address multiplicity issues are provided in Section 4.4.

The testing sequence will be:

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

The analysis plan of incidence of any ≥ Grade 2 peripheral neuropathy events will be described in Section 5.3.

4.2.1.1. ORR

The secondary efficacy endpoint of ORR is defined as the proportion of patients who achieve a confirmed PR or better (i.e., 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 for the primary analysis 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 two treatment arms (SVd versus Vd) will be performed using the Cochran-Mantel-Haenszel (CMH) test stratified by stratification factors including prior PI therapies, number of prior anti-MM regimens, and R-ISS stage at study entry. The CMH estimate of odds ratio and its 95% CI and p-value for testing treatment difference will be reported. The unadjusted number and percentage of patients achieving PR or better (i.e., PR, VGPR, CR, or sCR) will be summarized by treatment arm. 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 treated as non-responders. The forest plot of estimated odds ratio will be provided for each stratification factor.

In addition, the number and percentage of patients in the following response categories will be presented by treatment arm: stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD), progressive disease (PD), and not evaluable (NE). The corresponding 95% exact CI for each response category will also be provided.

Additionally, the following sensitivity analyses for ORR will be conducted on ITT population:

- Patients who have not had the opportunity to complete at least 2 scheduled post-C1D1 MM evaluations will be considered non-responders
- Comparison of ORR endpoint by treatment based on investigator's assessment

4.2.1.2. 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 primary 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.

4.2.2. Analyses of Non-Key Secondary Endpoints

The following non-key secondary endpoints will be summarized by treatment arm for ITT population, unless otherwise stated. If nominal p-values are computed for those secondary efficacy analyses, they should be interpreted with caution due to potential issues of multiplicity.

4.2.2.1. Overall Survival (OS)

The analysis of OS will be performed by treatment arm (SVd versus Vd) based on the stratified log-rank test. The strata will include prior PI therapies, number of prior anti-MM regimens, and R-ISS stage at study entry. If death event did not occur during the follow-up period, the patient is censored at the date of discontinuation from the study (i.e. withdrawal of consent), or date of last participating visit (e.g., a telephone contact with patient status being alive) on or before database cutoff date, whichever occurs first. The number and percentage of patients with death will be provided. Median OS time with 95% CI will be estimated based on the KM method for each treatment arm. The KM curve for OS will be provided. A non-stratified log-rank test will be performed as a supportive analysis.

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.

Since patients in the Vd arm are allowed to crossover to SVdX and SdX treatment after PD, adjustment for the effect of crossover on OS may be performed based on Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis (1991).

4.2.2.2. 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, by treatment arm along with their associated exact 95% CIs.

MRD will be assessed for patients who achieved CR or sCR by analyzing bone marrow aspiration. A status of positive vs. negative will be assigned. 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. The exact 95% CI will be provided.

4.2.2.3. Duration of Response (DOR)

DOR is defined for patients with a confirmed PR or better as the duration from the date of first IRC confirmed PR or better to the date of first IRC-confirmed PD or death due to any cause,

whichever occurs first. Please refer to Table 4-1 for details on the outcome and censoring definitions.

DOR will be performed by treatment arm (SVd versus Vd) based on the stratified log-rank test for patients with a IRC-confirmed PR or better. The strata will include prior PI therapies, number of prior anti-MM regimens, and R-ISS stage at study entry .The median DOR with 95% CI will be estimated based on the KM method. The KM curve for the DOR by treatment arm will be provided.

As supportive analyses, median DOR and 95% CI will be calculated based on KM method by treatment arm using PP population.

4.2.2.4. ORR1 (ORR for SVdX Population only)

ORR1 will be performed only on the SVdX population. Patients who cross over from Vd to SdX after IRC-confirmed PD will not be included. The percentage of patients achieving a confirmed PR or better (i.e., PR, VGPR, CR, or sCR) 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 and associated exact 95% CI will be summarized for SVdX population.

4.2.2.5. PFS1 (PFS for SVdX Population only)

PFS1 defined as the duration from the date of first SVdX treatment, after crossover from Vd arm, to the date of first IRC-confirmed PD, or death due to any cause will be performed for SVdX population. The patients in SVdX population without PD or death will be censored at the date of last disease assessment on or before database cutoff date. The outcome and censoring definitions for PFS1 are the same as those for PFS in Table 4-1.

The median PFS1 with 95% CI will be estimated based on the KM method. The KM curve for PFS1 will be provided.

4.2.2.6. Time to Next Treatment (TTNT)

TTNT is defined as the duration from date of randomization to start of next anti-MM treatment or death, whichever occurs first. For patients without an event, their follow-up time will be censored at the date of discontinuation from study, or last participating visit on or before database cutoff date, whichever occurs first.

TTNT analysis will be performed by treatment arm based on the stratified log-rank test. The strata will include prior PI therapies, number of prior anti-MM regimens, and R-ISS stage at study entry. Median TTNT with 95% CI will be estimated based on the KM method. The KM curve for TTNT will be provided.

4.2.2.7. Time to Response (TTR)

TTR is defined as duration from randomization to the date of first IRC-confirmed PR or better (i.e., PR, VGPR, CR, or sCR) before IRC-confirmed PD or initiating a new MM treatment per IMWG response criteria. The patients who do not achieve IRC-confirmed PR or better response will be censored at the date of last disease assessment on or before database cutoff date.

TTR analysis will be performed by treatment arm based on the stratified log-rank test. The strata will include prior PI therapies, number of prior anti-MM regimens, and R-ISS stage at study entry. The median TTR with 95% CI will be estimated based on KM method. The KM curve for TTR will be provided.

4.2.2.8. PFS2 (PFS for patients who received post-SVd/Vd/SVdX treatment)

PFS2 is defined as the duration from the date of first dose of post-SVd/Vd/SVdX treatment to the date of first PD on post-SVd/Vd/SVdX treatment, or death due to any cause. The patients who do not have any PD on post-SVd/Vd/SVdX treatment, or do not experience death will be censored at the date of last disease assessment on or before database cutoff date. The outcome and censoring definitions for PFS2 is the same as those for PFS in Table 4-1.

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.

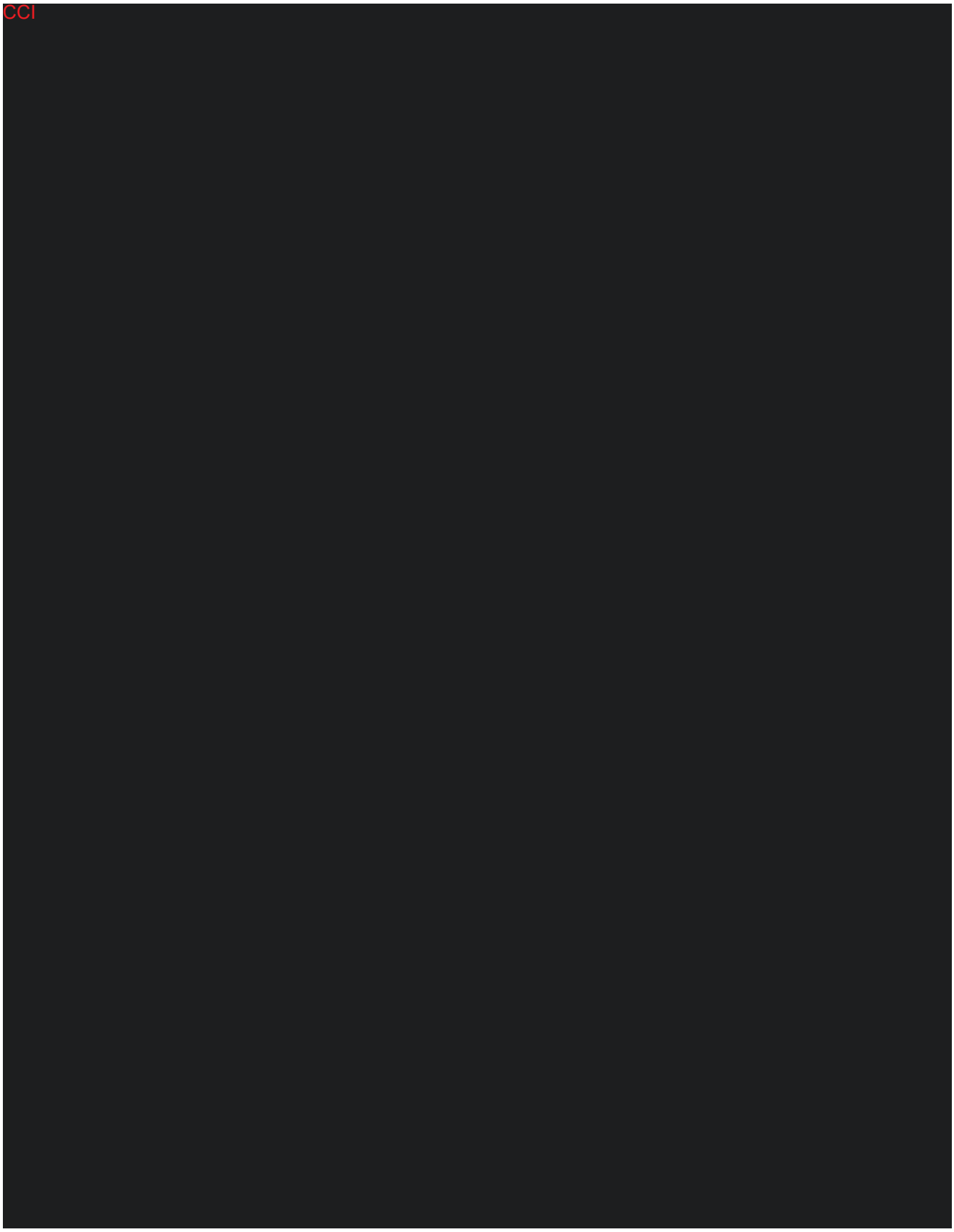
4.2.2.9. Chemotherapy-induced Peripheral Neuropathy (QLQ-CIPN20)

Patient-reported peripheral neuropathy will be assessed using the EORTC QLQ-CIPN20 instrument. The QLQ-CIPN20 instrument is a 20-item QoL instrument, which has been developed to elicit patients' experience of symptoms and functional limitations related to CIPN (Postma et al, 2005). The QLQ-CIPN20 has 3 subscales: a sensory, motor, and autonomic subscale. The QLQ-CIPN20 contains 20 items assessing sensory (9 items), motor (8 items), and autonomic symptoms (3 items). Using a 4-point Likert scale (1="not at all", 2="a little", 3="quite a bit", and 4="very much"), patients indicate the degree to which they have experienced sensory, motor, and autonomic symptoms during the past week. All scale scores are converted to a 0-100 scale, with higher scores indicating more symptom burden. The scale score will only be calculated if at least half of the items (i.e., 5 of 9 items, or 4 of 8 items) from the subscale have been answered.

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, stratification factors including prior PI therapies, number of prior anti-MM regimens, and R-ISS stage at study entry, and the baseline value of the corresponding subscale score as covariates, as well as random effect of patients and repeated measures over time points. The adjusted mean changes of each treatment arm as well as the treatment difference will be presented with 95% CI and p-value.

4.3. EXPLORATORY ANALYSES

CCI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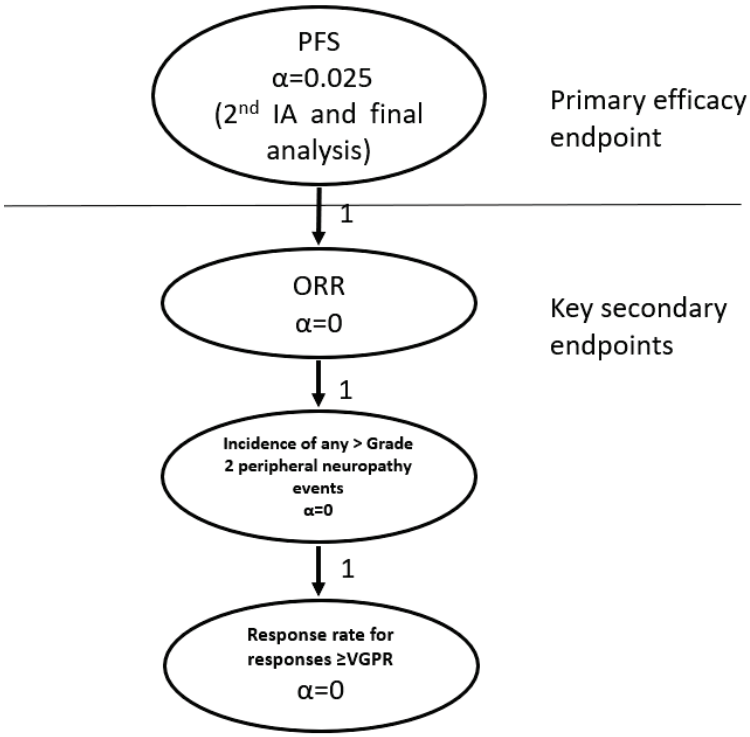
CCI

4.4. Multiple Comparisons/Multiplicity

The overall type I error for the primary endpoint and each key secondary endpoint is strictly controlled at 2.5% (one-sided).

The graphical multiple testing procedure in Bretz et al (2009) will be used to test the primary and key secondary endpoints. It is a Bonferroni-based closed test procedure, so it strongly controls the family-wise error rate across the endpoints. See the figure below for the alpha reallocation for the primary and key secondary endpoints. The weight for reallocation of the alpha is represented on the directed edges connecting hypotheses.

Figure 1: graphical illustration of the propagation of endpoint-specific alpha



Statistical significance of key secondary endpoints will not be claimed until the primary endpoint of PFS have reached significance. The key secondary endpoints will be tested using the hierarchical testing procedure as shown in Figure 1 to maintain the overall type I error.

5. SAFETY

Safety analyses will use the safety population with the outputs presented by the treatment arm and overall.

Safety analyses will be based on the reported AEs and other safety information, such as 12-lead electrocardiogram (ECG), vital signs, physical examination, ECOG performance status, ophthalmic exam, clinical laboratory assessments including hematology, serum chemistry, coagulation parameters, and urinalysis.

General rules

All safety analyses will be performed using the following common rules:

- Safety data in patients who do not belong to the safety population (e.g., enrolled but did not receive any dose of study treatment, partial or complete) will be listed separately.
- The baseline value is the last available value before the first dose of study treatment. Please also refer to Section 2.6 for additional information.
- The analyses of the safety variables will be essentially descriptive, and no statistical testing is planned except for the comparison of the incidence of any Grade ≥ 2 peripheral neuropathy events between the SVd Arm and the Vd Arm as one of the secondary objectives.
- Unscheduled visit measurements will be used for computation of baseline, worst and last values. The unscheduled visit measurements will also be included in data listings.
- Analysis for patients who cross over from the VD arm to the SVdX or SdX treatment will be summarized separately and details are provided in Section 5.8.

5.1. ADVERSE EVENTS

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

All AEs (including serious adverse events [SAEs]) will be coded to a preferred term (PT) and associated primary system organ class (SOC) using the MedDRA.

The severity of all AEs will be graded according to the NCI CTCAE Grading Scale, v. 4.03. An AE with a CTCAE grade of 3 or higher is considered a severe AE. The severity of the AE is different from the seriousness of the AE. For AEs not covered by CTCAE, the severity will be characterized as “mild,” “moderate,” “severe”, “life-threatening” (corresponding to Grades 1 to 4) according to the following definitions:

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

- Life-threatening.

5.1.1. Definition of Treatment-emergent Adverse Events(TEAE), Serious Adverse Events (SAE) and Treatment-emergent Treatment-related Adverse Events (TRAE)

Treatment-emergent adverse events (TEAE)

- Treatment-emergent adverse events (TEAE) are defined by the following for patients who are in the SVd or Vd arm, excluding those who cross over from the Vd Arm to the SVdX or SdX treatment:
    - SVd arm:
      Any event that was not present prior to the initiation of SVd treatment or any event already present that worsens in either intensity or frequency following exposure to SVd treatment, from the first dose of study treatment to 30 days after the last dose of SVd treatment inclusive, or the day before the start of a new anti-MM treatment, whichever occurs first. Additionally, any AEs that occurred 30 days after the last dose of SVd treatment or after the start of a new anti-MM treatment will also be considered as TEAE, if assessed by the Investigator as related to selinexor and/or bortezomib and/or dexamethasone.
    - Vd Arm:
      Any event that was not present prior to the initiation of Vd treatment or any event already present that worsens in either intensity or frequency following exposure to the Vd treatment, from the first dose of study treatment to 30 days after the last dose of study treatment inclusive, or the day before the start of a new anti-MM treatment, whichever occurs first. Additionally, any AEs that occurred 30 days after last dose of Vd treatment or after the start of a new anti-MM treatment will also be considered as TEAE, if assessed by the Investigator as related to bortezomib and/or dexamethasone.
- Treatment-emergent adverse events (TEAE) are defined by the following for patients who cross over from the Vd Arm to the SVdX or SdX treatment:
    - Vd Arm (before crossover):
      Any event that was not present prior to the initiation of Vd treatment or any event already present that worsens in either intensity or frequency following exposure to Vd treatment, from the first dose of Vd treatment to 30 days after the last dose of Vd treatment inclusive, or the first dose of SVdX or SdX treatment after crossover exclusive, whichever occurs first. Additionally, any AEs that occurred 30 days after last dose of Vd treatment and before the first dose of SVdX or SdX treatment after crossover will also be considered as TEAE, if assessed by the Investigator as related to bortezomib and/or dexamethasone.
    - After crossover to the SVdX treatment:
      Any event that was not present prior to the initiation of SVdX treatment or any event already present that worsens in either intensity or frequency following exposure to the first dose of SVdX treatment after crossover to 30 days after the last dose of SVdX treatment inclusive, or the day before the start of a new anti-

MM treatment, whichever occurs first. Additionally, any AEs that occurred 30 days after last dose of SVdX treatment or after the start of a new anti-MM treatment will also be considered as TEAE, if assessed by the Investigator as related to selinexor and/or bortezomib and/or dexamethasone.

- After crossover to the SdX treatment:
  Any event that was not present prior to the initiation of SdX treatment or any event already present that worsens in either intensity or frequency following exposure to the first dose of SdX treatment after crossover to 30 days after the last dose of SdX treatment inclusive, or the day before the start of a new anti-MM treatment, whichever occurs first. Additionally, any AEs that occurred 30 days after last dose of the SdX treatment or after the start of a new anti-MM treatment will also be considered as TEAE, if assessed by the Investigator as related to selinexor and/or dexamethasone.

Serious adverse events (SAE)

An SAE is any untoward medical occurrence, at any dose, that:

- Results in death
- Is life-threatening (i.e., 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
- Results in a congenital anomaly/birth defect

SAE needs to be clearly documented on the AE form. 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).

Treatment-emergent treatment-related adverse events (TRAE)

A TRAE is any TEAE that is related to study treatment, i.e., selinexor and/or bortezomib and/or dexamethasone.

Adverse event of clinical interest (AECI)

Any AE (serious or non-serious) 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.

5.1.2. Analysis Methods

The primary focus of AE reporting will be on TEAEs.

If an AE date/time of onset (occurrence or worsening) is incomplete, an imputation algorithm will be used to determine the AE as treatment-emergent. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment-emergent unless there is

definitive information to determine it is not treatment emergent. Details on classification of AEs with missing or partial onset dates are provided in Section 2.2.2.

AE summaries will include number (n) and percentage (%) of patients who have experienced an AE. The denominator for computation of percentages is the number of patients in the corresponding treatment arm. Multiple occurrences of the same event in the same patient will be counted only once in the tables.

Unless otherwise specified, sorting order will follow the alphabetic order in SOC, and further by decreasing frequency of PTs within each SOC. When more than one PT has same number of events, the order of presentation will be alphabetical in PTs.

Based on the entries on the eCRF AE page,

- An AE is considered related to study treatment if:
    - the entry for "Relationship to Selinexor" is "Related", or
    - the entry for "Relationship to Bortezomib" is "Related", or
    - the entry for "Relationship to Dexamethasone" is "Related".
- An AE is considered related to selinexor if the entry for "Relationship to Selinexor" is "Related".
- An AE is considered related to bortezomib if the entry for "Relationship to Bortezomib" is "Related".
- An AE is considered related to dexamethasone if the entry for "Relationship to Dexamethasone" is "Related".

The summary of AEs by causality will generally include the following categories of causality.

- Related to either selinexor or bortezomib or dexamethasone
- Related to selinexor only
- Related to bortezomib only
- Related to dexamethasone only
- Not related to selinexor or bortezomib or dexamethasone

5.1.3. Analysis of TEAE

An TEAE overview summary table will be provided, which will include the number of patients with at least one of the adverse events:

- TEAEs
- Grade 3/4 TEAEs
- Serious TEAEs
- TEAEs leading to dose modifications of study treatment
- TEAEs leading to dose reduction of study treatment
- TEAEs leading to dose interruption of study treatment

- TEAEs leading to study treatment discontinuation
- TEAEs leading to death
- TRAE
- Serious TRAEs
- TRAEs leading to dose modifications of study treatment
- TRAEs leading to dose reduction of study treatment
- TRAEs leading to dose interruption of study treatment
- TRAEs leading to study treatment discontinuation
- TRAEs leading to death

TEAEs will be summarized by primary SOC and PT and will include the following categories:

- All TEAEs
- All TEAEs, by causality
- All TEAEs, by maximum grade
- Grade 3 or higher TEAEs
- Grade 3 or higher TEAEs, by causality
- TEAEs leading to dose modifications of study treatment
- TEAEs leading to study treatment discontinuation

The most commonly reported (at least 10% of all patients) TEAEs will be presented by PT only and will include the following categories:

- The most commonly reported TEAEs
- The most commonly reported TEAEs related to study treatment

5.1.4. Analysis of SAE

Treatment-emergent SAEs will be summarized by primary SOC and PT and will include the following categories:

- All treatment-emergent SAEs
- All treatment-emergent SAEs, by causality
- Treatment-emergent SAEs leading to dose modifications of study treatment
- Treatment-emergent SAEs leading to study treatment discontinuation

All SAE will be provided in a data listing.

5.1.5. Analysis of AECI

Standard MedDRA Query (SMQ),Customized MedDRA Query (CMQ) will be utilized for AECI analysis. Analyses of treatment-emergent AECI will be performed separately for each

pre-specified AECI category. Overview summary of all AECI will be summarized similarly as in Section 5.1.3.

The following AECI will be summarized by PT:

- All TEAEs
- Serious TEAEs

The list of AECI categories are provided in Table 5-1. The search strategy of preferred terms for each category will be provided in a separate document.

Table 5-1 AECI Categories

Group Category	AECI Category
Hematologic events	Neutropenia
	Thrombocytopenia
Constitutional events	Decreased Appetite
	Weight Decreased
Eye disorders events	Blurred Vision
	Cataract
Gastrointestinal events	Nausea
	Vomiting
Infection	Pneumonia
	Opportunistic Infection
	Sepsis
Metabolism and nutrition disorders	Hyponatremia
Nervous system disorders	Neurological Toxicity
Others	Hepatobiliary Disorders
	Cardiac Toxicity

5.2. DEATH

The following summaries on death events will be provided:

- An overview of all death events and primary cause of death
- TEAEs leading to death (death as an outcome on the AE report page as reported by the Investigator), by primary SOC and PT
- TEAEs leading to death and are related to study treatment, by primary SOC and PT
- TEAEs leading to death and are related to selinexor only, by primary SOC and PT
- TEAEs leading to death and are related to bortezomib only, by primary SOC and PT
- TEAEs leading to death and are related to dexamethasone only, by primary SOC and PT
- Listing of all TEAEs leading to death
- Listing of all death events

5.3. PERIPHERAL NEUROPATHY EVENTS

The analysis of 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 have reached significance.

Treatment difference between the SVd and Vd Arm for the incidence of any Grade ≥ 2 peripheral neuropathy events will be tested using the Cochran-Mantel-Haenszel (CMH) test, stratified by Prior PI therapies (Yes or No); Number of prior anti-MM regimens (1 or >1); and R-ISS stage at study entry (R-ISS Stage III versus R-ISS Stage I or II). 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 the associated 2-sided 95% CIs. The Breslow-Day test will be performed as sensitivity analysis to assess homogeneity of odds ratios across the strata. A forest plot will be produced if the result of the Breslow-Day test is shown to be significant. The forest plot will show the estimated odds ratio with the associated 2-sided 95% CIs for each stratification factor. For patients who cross over from the Vd Arm to the SVd or SdX treatment, the analysis will only include peripheral neuropathy events that occurred prior to the crossover.

A sensitivity analysis will also be conducted to assess the treatment difference between the SVd and Vd Arm for the incidence of any Grade ≥ 2 peripheral neuropathy events using the CMH and Breslow-Day test on the safety population, in which all the peripheral events will be included regardless of the cross-over status of the patients who cross over from the Vd Arm to the SVdX or SdX treatment.

Similar analysis using the CMH test and the Breslow-Day test as described in the paragraphs above 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.

5.4. LABORATORY SAFETY VARIABLES

5.4.1. Definitions

Clinical laboratory data consists of blood analysis, including hematology, serum chemistry, coagulation parameters, and urinalysis. Clinical laboratory values in conventional units will be converted using the international system of units (SI).

The laboratory parameters will be classified as follows:

- Hematology (blood sample: whole blood + ethylenediaminetetraacetic acid [EDTA]) tests will include hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count, WBC differential, red blood cell count, lymphocytes, monocytes, neutrophils, eosinophils, basophils, and platelets. WBC differential may be automated or manual as per institutional standards.
- Complete Serum Chemistry will include sodium, potassium, chloride, bicarbonate, urea or blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphate, magnesium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, total protein, albumin, creatine kinase and urate.
- Coagulation parameters will include prothrombin time, international normalization ratio (INR), and activated partial thromboplastin time (aPTT).
- Urinalysis will include appearance, color, glucose, hemoglobin, ketones, pH, protein and specific gravity. Microscopy will only be performed if clinically indicated.

5.4.2. Analysis of Laboratory Variables

Whenever applicable, severity of selected clinical laboratory measures will be determined based on the CTCAE criteria. Laboratory values with CTCAE Grade ≥ 3 will be presented in a data listing. The worst toxicity grade in hematology and chemistry will be summarized by toxicity grade. Shift tables that present changes from baseline to worst on-study relative to CTCAE classification ranges will be presented. These shift tables will include results from unscheduled visits.

For several key laboratory parameters, box plots on measurements over time as well as by-patient plots for patient-level measurements over time may be presented.

A listing of cases where ALT or AST > 3x upper limit of normal (ULN) with simultaneous total bilirubin > 2x ULN will be presented.

Thresholds/Range analyses for selected laboratory parameters will be conducted. The number and percentage of patients classified into each category based on worst values will be presented.

5.5. VITAL SIGNS, ECOG, AND PHYSICAL EXAMINATION VARIABLES

Full physical examinations are performed only during screening and end-of-treatment (EoT) visits. At other visits, symptom-directed physical examinations are conducted if clinically indicated.

Vital signs include height (without shoes) in centimeters (cm) [measured during screening visit only], weight (indoor clothing without shoes) in kilograms (kg), body surface area (BSA), systolic and diastolic blood pressure (SBP and DBP), pulse measurements, and body temperature (°C). BSA will be calculated by the Dubois (Dubois and Dubois, 1916) Method.

An ECOG score assessment with grades 0-5 will be performed during screening, day 1 of each cycle, and EoT visit.

The actual value and change from baseline to each on-study evaluation will be summarized for vital signs including pulse, temperature, systolic blood pressure, diastolic blood pressure, BSA and weight. Shift tables that present changes from baseline to highest on-study and lowest on-study for systolic blood pressure and diastolic blood pressure will be presented. Shift tables that present changes from baseline to worst on-study and last on-study ECOG performance status values will also be produced.

Abnormal vital signs results will be summarized in the threshold/range analyses.

Abnormal PE findings will be provided in a data listing.

All vital sign measurements, physical examination results and ECOG performance status scores may also be provided in data listings.

5.6. ELECTROCARDIOGRAM (ECG)

Standard 12-lead ECGs will be performed during screening and prior to administration of study treatment on cycle 1 day 1, EoT visits, and if clinically indicated after cycle 1 day 1 but before EoT visits. Patients must rest for at least 5 minutes prior to the ECG recording. The Investigator will interpret the ECG using one of the following categories: normal, abnormal but not clinically significant, or abnormal and clinically significant. The following will be assessed: heart rate, PR interval, QRS interval, and QT corrected using Fridericia's formula (Fridericia, 1920).

Changes from baseline to highest on-study post baseline measurement for PR interval, QRS interval, and QT corrected will be summarized using shift tables. For heart rate, changes from baseline to lowest and highest on-study post baseline measurement will be presented.

Abnormal ECG results will be summarized in the threshold/range analyses.

Electrocardiogram data for each patient may also be provided in a data listing.

5.7. OPHTHALMIC EXAM

A full ophthalmic examination will be performed during the Screening and EoT visits, and if clinically indicated after cycle 1 day 1 but before EoT visits. Prior to dilation, best corrected visual acuity, slit lamp examination and tonometry will be conducted. Following dilation, fundoscopy slit lamp examination to document lens clarity will be performed. 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.

All ophthalmic examination findings will be presented in a data listing.

5.8. ANALYSES FOR PATIENTS WHO CROSS OVER

The following analyses will be repeated for patients who cross over from the Vd Arm to the SVdX or SdX treatment:

- Analysis of TEAE
    - TEAE overview summary
    - All TEAE summarized by SOC and PT, all TEAEs by causality, TEAEs leading to dose modifications in study treatment and TEAEs leading to study treatment discontinuation
- Analysis of SAE
    - All treatment-emergent SAE summarized by SOC and PT, all treatment-emergent SAE by causality
- Death
    - An overview of all death events and primary cause of death
    - TEAEs leading to death (death as an outcome on the AE report page as reported by the Investigator), by primary SOC and PT
- Analysis of Laboratory Variables, Vital Signs and Electrocardiogram
    - Shift tables as mentioned in Section 5.4.2, 5.5 and 5.6.

6. REFERENCES

Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. Statistics in medicine. 2009;28(4):586-604.

Cui L, Hung H, Wang S. Modification of sample size in group sequential clinical trials. Biometrics. 1999;55:853-857.

Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol. 2016;17(1):27-38.

DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Medicine. 1916;17:863-871.

EORTC QLQ-C30 Scoring Manual (3rd edition). Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. Brussels: EORTC, 2001. ISBN: 2-9300 64-22-6.

Fridericia L. Die Systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken. [The duration of systole in the electrocardiogram of normal subjects and of patients with heart disease.]. Acta Medica Scandinavica. 1920;53:469-86.

Van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health. 2012;15(5):708-15.

Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncology. 2016; 17(8): e328-e346.

Lan K, DeMets D. Discrete sequential boundaries for clinical trials. Biometrika. 1983;70:659-63.

Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol. 2015;33(26):2863-9.

Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. The New England journal of medicine. 2016;375(8):754-66.

Postma TJ, Aaronson NK, Heimans JJ, et al. The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: The QLQ-CIPN20. European Journal of Cancer. 2005;41(8):1135–1139.

Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using rank preserving structural failure time models. Commun Stat-Theor M. 1991;20(8):2609-31.

7. APPENDICE

7.1. Appendix I: Schedule of Assessments

Table 7-1 Schedule of Assessments and Study Activities

	Screening[2]	**C1**	**C1 Phone Call**	**MM Disease Assessment Visits**	**In-clinic Dosing Visits (> C1D2)**	**EoT Visit**[3]	**Safety Follow-up Call**	**Durability of Response and Survival Follow-up Visit**[4]
	D -28 to -1	**D1**[5]	**D3**[6] **(selinexor-containing regimens only)**			**≤ 14 Days Post-Last Dose**	**30 days after last dose of treatment**	**Every 3 months until End-of-Study**
Activity/Assessment[1]				**± 2 days**[7]	**± 2 days**		**+ 7 days**	**± 14 days**
ICF[8]	X							
Inclusion/Exclusion	X							
Demographics	X							
Medical History	X							
Clinical Assessments								
Height	X							
Weight	X	X			X[9] (D1 of each cycle only)	X		
BSA[10]	X	X						
Vital signs[11]	X	X		X[12]	X	X		
Complete PE	X					X		
Symptom-directed PE		Perform if clinically indicated		Perform if clinically indicated				Perform if clinically indicated
ECOG	X				X (D1 of each cycle only)	X		

	Screening[2]	**C1**	**C1 Phone Call**	**MM Disease Assessment Visits**	**In-clinic Dosing Visits (> C1D2)**	**EoT Visit**[3]	**Safety Follow-up Call**	**Durability of Response and Survival Follow-up Visit**[4]
	D -28 to -1	**D1**[5]	**D3**[6] **(selinexor-containing regimens only)**			**≤ 14 Days Post-Last Dose**	**30 days after last dose of treatment**	**Every 3 months until End-of-Study**
Activity/Assessment[1]				**± 2 days**[7]	**± 2 days**		**+ 7 days**	**± 14 days**
Ophthalmic examination	X[13]			Perform if clinically indicated		X		
12-lead ECG[12]	X[13]			Perform if clinically indicated		X		
Laboratory Assessments								
Urinalysis	X[13]					X		
CBC with differential	X[15]			X	X (C1D8 only)	X		
Complete serum chemistry	X	X		X	X (C1D8 only)	X		
Coagulation tests	X[13]					X		
Pregnancy test (if applicable)[i)]	X				X (D1 of each cycle only)	X		
C-reactive protein	X[13]					X		
PK at Selected Investigational Sites in North America Only (up to 25 patients per arm)								
Vd Arm subset: Blood draws for bortezomib PK testing					X (C2D11 only)[17]			
SVd Arm subset: Blood draws for bortezomib and selinexor PK testing					X (C2D15 only)[17]			

	Screening[2]	**C1**	**C1 Phone Call**	**MM Disease Assessment Visits**	**In-clinic Dosing Visits (> C1D2)**	**EoT Visit**[3]	**Safety Follow-up Call**	**Durability of Response and Survival Follow-up Visit**[4]
	D -28 to -1	**D1**[5]	**D3**[6] **(selinexor-containing regimens only)**			**≤ 14 Days Post-Last Dose**	**30 days after last dose of treatment**	**Every 3 months until End-of-Study**
Activity/Assessment[1]				**± 2 days**[7]	**± 2 days**		**+ 7 days**	**± 14 days**
Multiple Myeloma Disease Assessments [7,18]								
SPEP with serum protein immunofixation[19]	X	X		X		X		X
UPEP (24-hr urine) and urine protein immunofixation[19]	X	X		X		X		X
Quantitative Ig level[19]	X	X		X		X		X
Serum FLC[19]	X	X		X		X		X
β_2-microglobulin	X					X		
LDH	X[15]					X		
Skeletal survey[20]	X			Frequency determined by the Investigator		X		Perform if clinically indicated
Clinical plasmacytoma assessment[19, 21]	X	X		Perform if clinically indicated		X		Perform if clinically indicated
Bone marrow aspirate[23]	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[23]				At the time of response to confirm CR or sCR				

	Screening[2]	**C1**	**C1 Phone Call**	**MM Disease Assessment Visits**	**In-clinic Dosing Visits (> C1D2)**	**EoT Visit**[3]	**Safety Follow-up Call**	**Durability of Response and Survival Follow-up Visit**[4]
	D -28 to -1	**D1**[5]	**D3**[6] **(selinexor-containing regimens only)**			**≤ 14 Days Post-Last Dose**	**30 days after last dose of treatment**	**Every 3 months until End-of-Study**
Activity/Assessment[1]				**± 2 days**[7]	**± 2 days**		**+ 7 days**	**± 14 days**
HR-QoL[24]	X				X (D1 of each cycle only)	X		
Randomization	Prior to dosing of Vd/SVd							
Administration of study treatment		See Protocol Table 4, Table 5, Table 6, and Table 7		See Protocol Table 4, Table 5, Table 6, and Table 7	See Protocol Table 4, Table 5, Table 6, and Table 7[25]			
AE recording	Throughout							
SAE reporting	Throughout							
Concomitant medication recording		Throughout						
Nutritional consultation	X[13]							
Telephone contact			X[6]				X	
Collection of information regarding antineoplastic therapy used after EoT							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 ; 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 ; 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.

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

[2] 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.

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

[4] 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.

[5] SVdX/SdX patients will return to Cycle 1 for SVdX/SdX treatment.

[6] 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.

[7] 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 (e.g., C10D29).

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

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

[10] 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.

[11] 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.

[12] 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.

[13] 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.

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

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

[16] 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 and at the EoT Visit (serum hCG). Pregnancy testing may also be performed as clinically indicated during the study.

[17] Perform blood draws for PK analysis at the time points in Table 17 in the protocol. 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 in North America that can accommodate patients for up to 4 hours. Details for PK sample collection and processing can be found in the *Study Manual*.

[18] 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 of the protocol 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 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.

[19] 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.

[20] 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.

[21] 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.

[22] 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. 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.

[23] 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.

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

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