19 May 2022
EMA/620277/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nexpovio

International non-proprietary name: selinexor

Procedure No. EMEA/H/C/005127/II/0001/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
5-HT3	5-hydrosytryptamine
ADR	adverse drug reaction
AE	adverse event
AUC	area under the concentration versus time curve
$AUC_{0-\infty}$	area under the curve from the time of dosing extrapolated to infinity
BIW	twice weekly
CBR	clinical benefit rate
CI	confidence interval
CHMP	Committee for Medicinal Products for Human Use
C1D1	Cycle 1 Day 1
CL/F	clearance
CMA	conditional marketing authorization
CMQ	custom MedDRA query analysis
C_{max}	maximum plasma concentration
CR	complete response
CrCl	creatinine clearance
CSR	clinical study report
CYP	cytochrome P450
DDI	drug-drug interaction
DOR	duration of response
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
eIF4E	eukaryotic translation initiation factor 4E
EMA	European Medicines Agency
FDA	Food and Drug Administration
GSH	glutathione
GST	glutathione S transferase
HLM	human liver microsomes
HR	hazard ratio
HR-QoL	Health Related- Quality of Life
IC50	half maximal inhibitory concentration
IκB	inhibitor of NF-κB
IMWG	International Myeloma Working Group
IRC	Independent Review Committee
ISS	International Staging System
ITT	intent to treat

Abbreviation	Definition
IV	intravenously
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MRD	minimal residual disease
mRNA	messenger ribonucleic acid
NCCN	National Comprehensive Cancer Network
NF-κB	nuclear factor κB
OE	ophthalmological examination
NHL	non-Hodgkin's lymphoma
OR	odds ratio
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PI	proteasome inhibitors
PK	pharmacokinetic(s)
PN	peripheral neuropathy
PO	oral
PR	partial response
PT	preferred term
QoL	quality of life
QW	once weekly
R-ISS	Revised International Staging System for myeloma
RP2D	recommended Phase 2 dose
RR	relapsed or refractory
SAE	serious adverse event
SC	subcutaneously
sCR	stringent complete response
SCT	stem cell transplant/transplantation
Sd	selinexor plus dexamethasone
SdX	patients originally randomized to Vd who crossed over to Sd treatment
SINE	selective inhibitor of nuclear export
SmPC	Summary of product characteristics
SOC	system organ class
SVd	selinexor-bortezomib-low dose dexamethasone
SVdX	patients originally randomized to Vd who crossed over to SVd treatment
$t_{1/2}$	time to peak plasma concentration

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Karyopharm Europe GmbH submitted to the European Medicines Agency on 7 April 2021 an application for a group of variations.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB
B.II.z	B.II.z - Quality change - Finished product - Other variation	Type IB	I, IIIA and IIIB

Group of variations including an extension of indication for Nexpovio in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy and a quality variation for the addition of a new pack size (8 tablets) to align with the dose modification guidance for the new indication. Sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 6.5 of the SmPC are updated to reflect the new indication and the new pack size. In addition, the Type II variation is intended to fulfil the Specific Obligation agreed in the context of the Conditional Marketing Authorisation (CMA) of Nexpovio via the submission of results from the confirmatory Phase 3 study, KCP-330-023. Annex II is updated to reflect the completion of this Specific Obligation. The Labelling and Package Leaflet are amended accordingly. The RMP (v 1.1) is amended consequently.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0384/2018 on the granting of a (product-specific) waiver.

The Paediatric Committee, having assessed the waiver application in accordance with Article 13 of Regulation (EC) No 1901/2006 as amended, recommended to grant a product-specific waiver for all subsets of the paediatric population in accordance with Article ll(l)(c) of said Regulation, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients. The paediatric investigation plan waiver was granted for selinexor as a treatment of MM as of 6 December 2020.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH sought scientific advice from the CHMP in September 2016 regarding the design of the global

phase 3 BOSTON study. Questions pertained to (key) study design features including the proposed patient population, selected dose regimens for the experimental and control arms, primary and secondary endpoints, PROs and statistical aspects (including sample size assumptions and planned interim analyses). A question regarding the safety database expected at the time of submission was also included as well as a question regarding regulatory options for approval. According to the MAH the protocol was modified to incorporate the feedback received from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Blanca Garcia-Ochoa Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	7 April 2021
Start of procedure	24 April 2021
CHMP Rapporteur's preliminary assessment report circulated on	9 July 2021
PRAC Rapporteur's preliminary assessment report circulated on	29 June 2021
PRAC RMP advice and assessment overview adopted by PRAC on	8 July 2021
Updated CHMP Rapporteur's assessment report circulated on	17 July 2021
Request for supplementary information (RSI) adopted by the CHMP on	22 July 2021
MAH's responses submitted to the CHMP on	10 September 2021
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	26 November 2021
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	26 November 2021
PRAC RMP advice and assessment overview adopted by PRAC on	2 December 2021
Updated CHMP Rapporteur's assessment report on the MAH's responses circulated on	10 December 2021
2nd Request for supplementary information (RSI) adopted by the CHMP on	16 December 2021
MAH's responses submitted to the CHMP on:	22 December 2021
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	3 March 2022
Updated CHMP Rapporteur's assessment report on the MAH's responses circulated on	21 March 2022
3rd Request for supplementary information (RSI) adopted by the CHMP on	24 March 2022
MAH's responses submitted to the CHMP on:	4 April 2022
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	8 May 2022
Updated CHMP Rapporteur's assessment report on the MAH's responses circulated on	13 May 2022
CHMP Opinion	19 May 2022
The CHMP adopted a report on similarity of Nexpovio with Imnovid,	19 May 2022

Timetable	Actual dates
Farydak, Ninlaro, Darzalex, Kyprolis, Blenrep, Abecma and CARVYKTI on	

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Multiple myeloma is a malignant plasma cell disorder that is characterized by the production of monoclonal immunoglobulin in a majority of patients and that invades adjacent bone tissue. Common manifestations include bone pain, renal insufficiency, hypercalcemia, anaemia, and recurrent infections.

Multiple myeloma is characterized by osteolytic lesions, usually in the pelvis, spine, ribs, and skull. Lesions are caused by expanding plasmacytomas or by cytokines secreted by myeloma cells that activate osteoclasts and suppress osteoblasts. Increased bone loss may also lead to hypercalcemia. Solitary extraosseous plasmacytomas are unusual but may occur in any tissue, especially in the upper respiratory tract. In many patients, renal failure is present at diagnosis or develops during the course of the disorder and is caused by the deposition of light chains in the distal tubules or by hypercalcemia. Patients also often develop anaemia due to kidney disease or suppression of erythropoiesis by cancer cells, but sometimes also due to iron deficiency. These signs and symptoms are commonly denoted as CRAB.

Claimed therapeutic indication

NEXPOVIO (selinexor) in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Epidemiology and risk factors, screening tools/prevention

MM is a rare and incurable plasma cell neoplasm which typically affects adults mostly over 60 years of age. The median age at diagnosis is 65–70 years; only 2% of patients are younger than 40 years (Raab 2009).

Multiple myeloma (MM) accounts for 1%-1.8% of all cancers and is the second most common haematological malignancy (after non-Hodgkin's lymphoma [NHL]) with an estimated incidence in Europe of 4.5-6.0/100 000/year, with approximately 176.404 new MM cases and 117,077 deaths due to MM anticipated in 2020 worldwide (The Global Cancer Observatory 2020).

The treatment of MM has notably progressed with the availability of new drugs and its combinations, such way that survival of patients with newly diagnosed multiple myeloma has increased from approximately 3 years in the years 1985 to 1998 (Kyle 2003) to 6 to 10 years (Moreau 2015) along the last 15 years. Despite the significant improvement in patients' survival over the past 20 years, only 10%-15% of patients achieve or exceed expected survival compared with the matched general population.

Biologic features, aetiology and pathogenesis

As previously described, MM is characterized by the increased proliferation of malignant monoclonal plasma cells in the bone marrow, with the subsequent bone marrow failure due to replacement of normal bone marrow haematopoiesis, the over-production of monoclonal immunoglobulins (M-protein, either intact immunoglobulins and/or free light chains [FLC]) which could be detected in the serum or urine, and finally the presence of systemic symptoms named as CRAB (hyperCalcemia, Renal impairment, Anaemia and Bone lesions). Increased susceptibility to infections (immunoparesis) and neurological complications are also present (Palumbo 2011).

Based on karyotype, MM is classified as non-hyperdiploid and hyperdiploid, with the latter accounting for 50% to 60% of cases and characterized by trisomies in odd-numbered chromosomes. MM has a heterogeneous progression pathway, with multiple relapses over time, whereby several MM cell subclones coexist at baseline and compete for dominance over time, leading to the evolution of drug-resistance clones [Laubach, 2014].

Drug resistance to prior regimens in patients with relapsed/refractory (RR) MM is due to continuous changes in the disease biology, in which a higher proportion of malignant cells are expressing a more aggressive, highly proliferative phenotype over time (Anderson, 2008).

Clinical presentation, diagnosis and stage/prognosis

The most common symptoms in MM patients include persistent skeletal pain, pathological fractures and vertebral collapse, anaemia, renal impairment, hypercalcaemia and recurrent or persistent bacterial infections. Approximately 20% of patients are asymptomatic at the time of diagnosis.

The most common criteria used in diagnosis of symptomatic MM is the presence of neoplastic plasma cells comprising more than 10% of BM cells or the presence of plasmacytomas, together with a monoclonal paraprotein (M-protein) in the serum and/or urine and the evidence of related organ or tissue impairment due to clonal plasma cell hyper-proliferation.

The International Staging System (ISS) is used for prognosis and it was revised by The International Myeloma Working Group (IMWG) including cytogenetics by fluorescence in situ hybridization (FISH) and lactate dehydrogenase (LDH, Revised International Staging System for Multiple Myeloma, R-ISS), and is now widely accepted (Palumbo, 2015). At the time of diagnosis, patients are categorized according to R-ISS, their age, comorbidity and their suitability for intensive treatment.

Despite advance in therapy, MM remains incurable. All patients eventually relapse and with each successive relapse, the chance of response and duration of response typically decreases and ultimately the disease becomes refractory and results in cumulative end organ damage (e.g., renal, cytopenias, infections and bone complications).

Management

Current treatment of MM includes glucocorticoids (dexamethasone, prednisolone, methylprednisolone), chemotherapy, primarily alkylating agents, including high dose chemotherapy followed by autologous stem cell transplantation (ASCT), proteasome inhibitors (PIs, such as bortezomib, carfilzomib and ixazomib), immunomodulatory agents (such as thalidomide, lenalidomide and pomalidomide), monoclonal antibodies (mAbs, such as daratumumab, isatuximab and elotuzumab) and the histone deacetylase inhibitor panobinostat.

The choice of therapy in the relapse setting depends on several parameters such as age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy and the

type of relapse (i.e. clinical versus biochemical relapse; in the case of biochemical relapse, treatment can be delayed).

At the time of first relapse and beyond, lenalidomide in combination with dexamethasone and bortezomib, either alone as single-agent or in combination with PEGylated doxorubicin were the available approved options until 2015. Bortezomib is mostly used in combination with dexamethasone in the relapse setting.

Panobinostat in combination with bortezomib and dexamethasone, is now indicated for the treatment of patients with RR MM who have received at least two prior regimens including bortezomib and an immunomodulatory agent. Carfilzomib has also been approved in combination with lenalidomide and dexamethasone and also in combination with dexamethasone alone in patients with at least one line of prior therapy. That is also the case of elotuzumab in combination with lenalidomide and dexamethasone and ixazomib in combination with lenalidomide and dexamethasone, all in patients who have received at least one prior line of therapy.

In very advanced-stage disease, pomalidomide in combination with low-dose dexamethasone, is approved in patients who have received at least two prior therapies, including both lenalidomide and bortezomib, and whose disease progressed after treatment with these medicines.

In young patients, a second ASCT may be considered, provided that the patient responded well to the previous ASCT and had a PFS of more than 24 months. In the relapse setting, allogeneic SCT should only be carried out in the context of a clinical trial. Therapies with a multimodal MoA, which target MM cells and elicit an immunogenic response, as well as drugs with new mechanisms of action, are expected to minimize the development of drug resistance in MM and/or increase disease response to therapy.

2.1.2. About the product

Selinexor (KPT-330) is an oral, slowly reversible covalent, selective inhibitor of nuclear export (SINE) compound that specifically blocks the nuclear export protein 1 (XPO1.) XPO1 is responsible for the unidirectional export of ~220 different cargo proteins from the nucleus to the cytoplasm (Garg 2017, Xu 2010, Xu 2012). The anti-neoplastic activity of SINE compounds is mediated through at least 3 distinct pathways involving tumour suppressor proteins (TSPs), oncoproteins, and the glucocorticoid receptor.

Selinexor synergizes with PIs such as bortezomib (Turner 2013, Turner 2016, Tai 2014, Wu 2016) and carfilzomib (Kandarpa 2013, Rosebeck 2016) leading to inhibition of cell proliferation and induction of MM cell death.

The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for the conditional marketing authorization (CMA) for NEXPOVIO (selinexor) in combination with dexamethasone for the treatment of MM in adult patients who have received at least 4 prior therapies and whose disease is refractory to at least 2 proteasome inhibitors, 2 immunomodulatory agents and an anti-CD38 MoA, and who have demonstrated disease progression on the last therapy (EPAR EMA/CHMP/95252/2021; 27/052021).

Nexpovio received a conditional marketing authorisation valid throughout the EU on 26 March 2021.

Selinexor was originally designated as an Orphan Medicinal Product in the European Union on 19 November 2014 - EU/3/14/1355. This product was withdrawn from the Union Register of orphan medicinal products by the European Commission in February 2021 upon request of the marketing authorisation holder at the time of the granting of a marketing authorisation. This product is no longer an orphan medicine.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The Applicant sought scientific advice from the CHMP in September 2016 regarding the design of the global phase 3 BOSTON study, see section 1.

2.1.4. General comments on compliance with GCP

The MAH states that study KCP-330-023 (BOSTON) was designed, implemented, and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with the applicable local regulations (including European Directive 2001/20/EC and United States [US] Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

At the time of initial MAA, a routine GCP inspection was requested by the CHMP. Two investigator sites in Greece and USA and the sponsor site in USA were inspected in March 2019. Several critical and major findings were detected which were system and process related.

"A GCP system inspection of the sponsor is necessary to confirm that those critical aspects found during this inspection are not repeated in other trials where Karyopharm is the sponsor."

Taking the above into account, it was considered justified to request a GCP inspection. One investigator site (in Barcelona, Spain) and the sponsor site (in Boston, US) were inspected on December 2021 and January 2022, respectively. The final Integrated Inspection Report (IIR) was made available on 17th March 2022. During this second GCP inspection it was concluded that even though significant improvements had been implemented since the previous EMA inspection there was still room for improvement in the quality management system of the Sponsor. Several critical findings were identified during the inspection. These aspects were satisfactorily addressed by the MAH during the procedure (see efficacy discussion).

2.2. Non-clinical aspects

The MAH submitted only new data related to the environmental risk assessment (ERA) for selinexor. No additional non-clinical information (pharmacology, pharmacokinetics or toxicology) was submited.

2.2.1. Introduction

The MAH submitted information for ERA of selinexor in accordance with EMEA/CHMP/SWP/4447/00 Corr 2 guidance. This information would not modify the current SmPC.

2.2.2. Pharmacology

N/A

2.2.3. Pharmacokinetics

N/A

2.2.4. Toxicology

N/A

2.2.5. Ecotoxicity/environmental risk assessment

The MAH has presented data for the phase I assessment of ERA (log Kow and PECsw).

Persistence, bioaccumulation and toxicity

LogKow (LogP at neutral Ph 7.0) of selinexor was measured by the shake-flask method (OECD 107). Prediction of Log P value was made using ACD/Labs software v12.5.

The experimental LogP of selinexor at neutral pH was 3.73 (predicted: 2.9).

Both predicted and measured LogKow of selinexor is < 4.5 so that screening for persistence, bioaccumulation and toxicity is not required.

Calculation of the Predicted Environmental Concentration (PEC)

PEC value was estimated in line with the formula provided in the ERA guideline. For selinexor, the following assumptions were made:

DOSEai = 100 mg /7 = 14.3 mg/day (calculated from the dose of 100 mg to be administered once weekly)

Fpen = 1.8/10,000 (=prevalence of plasma cell myeloma in the EU),

WASTEWinhab = 200 l/(inhabitant x day), the default value recommended in the guideline,

DILUTION = 10, the default value recommended in the guideline.

The PECsurfacewater of selinexor is 0.00129 µg/L and thus below the action limit of 0.01 µg/L. A phase II for selinexor would not be required.

2.2.6. Discussion on non-clinical aspects

Selinexor PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Therefore, selinexor is not expected to pose a risk for environment.

2.2.7. Conclusion on the non-clinical aspects

Considering the above data, selinexor is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Summary of studies supporting the clinical pharmacology of selinexor

Study No. Acronym Phase	Study Design/ Key Objectives	Population / N (treated)	Treatment	Status
KCP-330-001 Phase 1	Multicenter, open-label, dose escalation study Evaluate PK, PDn, antitumor response, OS, and tolerability of selinexor Determine the RP2D	Pts with advanced HM N = 285	Selinexor: Doses range from 3 mg/m^2 to 80 mg/m^2 or a fixed dose up to 80 mg Regimens: 3-week and 4-week cycles, with QW or BIW, or QoD×3 (Weeks 1 and 3) and BIW (Weeks 2 and 4)	Completed
KCP-330-002 Phase 1	Multicenter, open-label, dose escalation study Evaluate safety and tolerability, recommend RP2D Determine PK and PDn Describe antitumor response	Pts with advanced or metastatic solid tumor malignancies N = 189	Selinexor ranging from 3 to 85 mg/m^2 dosing QW, BIW or QoD×3 (Weeks 1 and 3) and BIW (Weeks 2 and 4) 21- or 28-day cycles	Completed
KCP-330-003 Phase 1b	Multicenter, randomized, open-label, 2-phase study Determine effects of high- and low-fat food on PK of selinexor tablet vs. capsules Compare PK of 3 selinexor formulations Evaluate tumor response Assess safety and tolerability	Pts with metastatic, locally advanced, unresectable, or locally recurrent soft tissue or bone sarcoma N = 54	Selinexor 30 or 50 mg/m^2 or 60 mg BIW 3 different formulations: capsules, tablets (both 1st and 2nd generation), and a liquid suspension (3 mg/mL) 4-week cycles	Completed

Study No. Acronym Phase	Study Design/ Key Objectives	Population / N (treated)	Treatment	Status
KCP-330-008 SOPRA Phase 2	A Randomized, Open-Label, Phase 2 Study of the Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330) Versus Specified Physician's Choice in Patients ≥ 60 Years Old with Relapsed or Refractory Acute Myeloid Leukemia (AML) Who Are Ineligible for Intensive Chemotherapy and/or Transplantation	Pts with RR AML ≥60 years of age who are ineligible for intensive chemotherapy and/or transplantation N = 213[a]	Selinexor Dose Regimen: 60 mg fixed dose or 55 mg/m^2 BIW, 4-week cycle Control arm: One of the following: • BSC including blood product transfusions, antimicrobials, and growth factors • BSC + low dose AraC • BSC + hypomethylating agent	Completed
KCP-330-009 SADAL Phase 2b	Open-label, multicenter, low- vs. high-dose study Evaluate efficacy (ORR, DOR, DCR) of study treatment Assess safety profile of study treatment	Pts with RR DLBCL N = 267	Low dose: Selinexor 60 mg, BIW, 4-week cycle High dose: Selinexor 100 mg BIW, 4-week cycle	Completed

Study No. Acronym Phase	Study Design/ Key Objectives	Population / N (treated)	Treatment	Status
KCP-330-010 SIRRT Phase 2	Single-arm, open-label study Determine ORR, DOR, DCR, PFS, OS, QoL Evaluate toxicity of selinexor	Pts with initial or RR RT N = 26	Selinexor 60 mg BIW, 4-week cycle	Completed
KCP-330-012 STORM Phase 2b Part 2 (Pivotal analysis)	Open-label, single-arm study Primary: Evaluate ORR Secondary: Evaluate DOR, CBR, DCR, PFS, TTP, TTNT, OS, and QoL Evaluate safety and tolerability	Pts with penta-refractory MM N = 123	Selinexor 80 mg + dexamethasone 20 mg BIW (Days 1 and 3 for Weeks 1 to 4), 4-week cycles	Completed

Study No. Acronym Phase	Study Design/ Key Objectives	Population / N (treated)	Treatment	Status
KCP-330-012 STORM Phase 2b **Part 1** (Supportive analysis)	Secondary: Evaluate efficacy (ORR, DOR, CBR, DCR, PFS, TTP, TTNT, OS; analyzed separately for patients with quad- or penta-refractory MM), QoL, and PK Evaluate safety and tolerability	Pts with quad- or penta-refractory MM N = 79	Selinexor 80 mg + dexamethasone 20 mg BIW (Days 1 and 3 for Weeks 1 to 3), 4-week cycles	Completed

2.3.2. Pharmacokinetics

Analytical methods

Bortezomib Matrix Lot-Dependent Stability Investigation

Covance Study Number 8413-691

To analyze bortezomib plasma samples from clinical study KPT-330-023, development and validation of a method to analyze bortezeomib in human plasma (K_2EDTA) was performed under Covance study number 8413-691. During method development, it was determined that bortezomib is not stable when stored at -70 ºC or -20 ºC in selected lots of K_2EDTA human plasma or Na-Heparin human plasma. Based on the method development data, it was determined that pretreatment of samples with formic acid (2%) is essential to stabilize bortezomib. Details of the stability experiments and results are summarized in this report.

The bortezomib instability was observed in accuracy and precision tests. When a previously qualified QC batch was re-tested (with curves prepared on the day of extraction in a later run) after having been stored at -20 ºC, the result failed to meet acceptance criteria due to low bias.

A summary of the investigation is presented in the table below.

Overall Study purpose	Investigate the cause of Bortezomib instability in human plasma
Impact of anticoagulant	K2EDTA and NaHeparin
Impact of temperature	-70 °C, -20 °C, 1-8 °C and room temperature
Impact of pH in human plasma	Pooled Human plasma treated with FA and pooled human plasma (NaHep) treated with FA
Impact of enzyme activity in human plasma	pooled Human plasma treated with heat and pooled human plasma (NaHep) treated with heat
Impact of individual human plasma	Untreated individual human plasma (K2EDTA)
QC evaluated	One set of HQC and LQC at each condition tested

To test whether the instability was caused by storage conditions

The result shows that the QC's and curves that were prepared on the day of run 17 extraction met the acceptance criteria. All the QC's qualified in run 12 and run 16 failed to meet acceptance criteria except for MQC 16. QC 13 is further biased low comparing to QC16. These results demonstrate that bortezomib is unstable in human plasma K_2EDTA. However, the failure of QCs was not due to storage conditions (-20 °C or -70 °C) of the samples.

To test Bortezomib stability in untreated and treated pooled human plasma K_2EDTA or Na Heparin

Human plasma K_2EDTA and human plasma Na-Heparin were treated with Formic Acid (2% FA in human plasma) to alter matrix pH value or heated in 50 ºC for two hours to inhibit possible enzyme activity. HQC and LQC were prepared in these matrixes to test Bortezomib stability. After having been qualified in each matrix, the fresh prepared HQC and LQC were aliquoted to be stored at -70 ºC, -20 ºC, on ice and at room temperature. These samples were tested on a later day with a second set of HQC/LQC freshly spiked and processed in the same quantification runs.

The results demonstrated in untreated human plasma Na-Heparin, bortezomib degraded the same way as in human plasma K_2EDTA in previous runs. Heat treatment did not stabilize bortezomib. However, when the matrix was treated with final FA content of 2%, the stability was greatly improved compared to the untreated: in human plasma Na-Heparin containing 2% FA, both QC aliquot stored at -20 ºC and -70 ºC met the acceptance criteria, but not the ones stored at 5 ºC or room temperature.

In human plasma K_2EDTA, the HQC and LQC met the acceptance criteria after been stored at -20 ºC or -70 ºC, which is inconsistent with earlier observation. Heat treatment did not further improve the stability comparing to untreated. In contrast to FA treated matrix, QC's met the acceptance criteria in all storage condition besides RT, which is ~28% low bias.

To understand the instability in untreated individual human plasma K_2EDTA

There were more than two lots of K_2EDTA matrixes used during MD. In at least two lots, bortezomib did not exhibit stability at -20 ºC or -70 ºC. In troubleshooting experiments, 20 individual lots of human plasma K_2EDTA were used to prepare HQC and LQC together with one of the pooled matrix lot used in MD and the lot used in matrix treatment test mentioned above. The qualified QC was then stored at -20 ºC and -70 ºC to be tested 48 hours later with HQC and LQC prepared again with the same lot on the day of extraction.

Different levels of stability were displayed in the 20 individual lots after been stored. In total, 6 lots out of 20 failed after being stored at -70 ºC for 48 hours revealing degradation of 19-56% in HQC and 14-48% in LQC. After being stored at -20 ºC, HQC and LQC prepared in 9 individual lots met the acceptance criteria, while the other 11 lots either failed at HQC or both concentrations.

In conclusion, the investigation into bortezomib instability in human plasma K_2EDTA indicates that bortezomib can be unstable in certain untreated human plasma K_2EDTA. The observed instability is dependent on unknown interactions in human plasma K_2EDTA. In some individual matrix lots, bortezomib was stable after 48 hours of storage at -20 ºC or -70 ºC. Pretreatment with formic acid is needed to stabilize bortezomib in K_2EDTA (stored at 5 ºC, -20 ºC or -70 ºC) or NaHeparin (stored at -20 ºC or -70 ºC) human plasma.

The report is to summarize the observations leading to the final assessment that the study samples could not be analyzed in a regulated study (KPT-330-023).

Absorption

Selinexor is orally bioavailable. The absorption is moderately rapid with a median time to the peak plasma concentration (tmax) of 2 to 4 hours. The consistent tmax across the range of doses evaluated (3 to 85 mg/m^2) suggests dose-independent absorption. Although selinexor is a low soluble compound, it exhibited high permeability in Caco-2 cells. The absolute bioavailability has not been conducted in humans. Oral bioavailability of selinexor in mice, rats, and monkeys is high, and allometric scaling is consistent with high oral bioavailability in humans.

Distribution

The distribution of selinexor is driven by plasma protein binding, which is approximately 95% and is not concentration dependent within the clinically relevant range. The blood to plasma ratio was less than 1, suggesting minimal association with red blood cells. The apparent central volume of distribution (Vc/F) was 113 L and the apparent peripheral volume of distribution (Vp/F) was 20 L (corresponding to an apparent volume of distribution at steady state [Vss/F] of 133 L or approximately 2 L/kg, assuming a 65 kg mass). The Vss/F exceeded the total body water (approximately 40 L), consistent with distribution of selinexor into tissues.

Elimination

Metabolism

Since the initial MAA submission of selinexor, no new information has been obtained regarding the metabolism of selinexor. The results summarized below were previously presented in the initial MAA submission.

Selinexor, as unchanged parent, is the major circulating moiety in human plasma. The most common circulating metabolite (<5% of peak of parent levels) is the trans-isomer of selinexor, designated KPT-375. This isomer, which likely derives from cis-trans isomerization of selinexor, has approximately 10% of the XPO1 inhibiting activity of selinexor and no other known biological properties. In plasma, other metabolites individually accounted for less than 1% of parent at peak selinexor plasma concentrations.

In human faeces, the predominant metabolite observed was KPT-452 (N-dealkylation; inactive metabolite), which is catalyzed by cytochrome P450 (CYP)3A4. In human urine, the primary metabolite observed was KPT-5000 (cysteine adduct; inactive metabolite), which is catalyzed by glutathione s-transferase (GST).

Selinexor was metabolically stable in human liver microsomes (HLM) and hepatocytes. In reaction phenotyping for CYPs and uridine 5'-diphospho-glucuronosyltransferases (UGTs), limited metabolism of selinexor was observed and was catalyzed only by CYP3A4 and multiple UGTs. Similar to observations in humans, in nonclinical species, including radio-profiling in rats and cold metabolism in monkeys, low levels of circulating metabolites were observed and unchanged selinexor was the primary (>90%) circulating moiety. The metabolites observed in excreta of nonclinical species were similar to those observed in humans.

Thus, parent selinexor is the main moiety in plasma and the limited metabolism of selinexor is catalyzed by multiple enzymes, including CYP3A4, UGTs, and GSTs. Importantly, the metabolites include KPT-375 (which has minimal biological activity), and at lower levels, inactive products of N-dealkylation, glucuronidation, and glutathione (GSH) conjugation. Thus, the contribution of metabolites to the pharmacological activity of selinexor is negligible.

Excretion

Based on quantitation of selinexor in human urine in Study 003, urinary excretion is a minor elimination pathway for selinexor. In the rat mass balance and quantitative whole-body autoradiography study, total recovery was 93% suggesting minimal long-term retention, selinexor was found to be excreted primarily by the hepatobiliary route into faeces with minimal excretion in urine (<1% unchanged parent). The terminal phase half-life (t½) of selinexor is approximately 6 hours and apparent clearance (CL/F) is 18.4 L/h.

Dose proportionality and time dependencies

In dose escalation studies in patients with advanced hematologic and solid tumour malignancies (Study 001 and 002, respectively), selinexor exhibited linear PK, demonstrating dose-proportional increase in exposure area under the concentration versus time curve [AUC] and maximum observed concentration [Cmax]). Selinexor was dosed 2 or 3 times weekly as a single agent and no substantial accumulation was evident following repeat dosing. At the 100 mg dose, the mean Cmax was 693 ng/mL and the mean AUC0-∞ was 6998 ng·h/mL (Study 001).

Food effects

The presence of food (high- or low-fat meals) delayed selinexor absorption (tmax from 1.7 to approximately 4 hours), however, there was minimal impact on exposures (geometric mean ratio [GMR] ranged between 114.7% and 125.5%) and this was not clinically relevant (Study 003). Meals with high- or low-fat content did not have a substantial effect on selinexor PK parameters. Therefore, selinexor should be taken with fluids and can be administered with or without food. The above results on food effect were previously presented in the initial MAA.

Bioequivalence

Selinexor exposure following oral administration of all tested formulations was considered to be functionally bioequivalent.

Tablet formulation 2.2 (also known as TF2.2) and several other formulations were tested in Study 003: hard-gelatin capsules, first-generation tablets (also known as tablet formulation 1 or TF1) and TF2.2, and a suspension formulation (prepared from TF1). All 3 formulations tested in Study 003 were considered to be functionally bioequivalent based on AUC from the time of dosing to time t (AUC0-t) and AUC from the time of dosing extrapolated to infinity (AUC0-∞). The second-generation tablet TF2 was developed in preparation for registration and commercial batches of formulation. There is clinical tablet formulation (TF2.2) and the commercial/clinical formulation (TF2.3). The only difference in the TF2.3 relative to TF2.2 is the removal of the trace yellow-colour pigment tartrazine from the outer top-coat, as a Scale-up and Post Approval Change (SUPAC) Level 1 change (FDA Guidance for Industry 1995). TF2.3 was found to exhibit similar in vitro dissolution performance with TF2.2 in f2 testing.

Pharmacokinetic in the target population

The population PK model was first developed and submitted with the initial MAA. The model was updated based on data from 793 patients across 7 clinical studies (second population PK model, Report MS-001) which was provided during the initial MAA procedure.

Population PK model in patients with DLBCL and other cancer types

Dataset

Table 1 Summary of Studies Included in the Analysis

Protocol/Population (N)	Description	Treatment	PK samples
KCP-330-001 Phase 1 Pts with advanced hematological malignancies (N = 285, 81 pts with MM)	A Phase I Study of the Safety, Pharmacokinetics and Pharmacodynamics of Escalating Doses of the Selective Inhibitor of Nuclear Export/SINE™ Compound KPT-330 in Patients with Advanced Hematological Malignancies	Selinexor Dose: ranging from 3 mg/m^2 to 80 mg/m^2 or a fixed dose up to 80 mg Regimens: 3-wk and 4-wk cycles, with QW or twice weekly, or QoD×3 (Wks 1 and 3) and twice weekly (wks 2 and 4)	Schedule 1 to 5: Days 1, 2, 3, 15/17 of cycle 1. Day 15/17 of cycles 2 and 3. Schedule 7: Days 1 of cycles 1, 2 and 3. Schedule 8: Days 1 and 8 of cycle 1. Day 1 of cycles 2 and 3. Schedule 9: Days 1, 2 and 3 of cycle 1. Day 1 of cycles 2 and 3.
KCP-330-002 Phase 1 Pts with advanced or metastatic solid tumor malignancies (N = 189)	Safety Study of KPT-330 in Patients with Advanced or Metastatic Solid Tumors	Selinexor Dose: ranging from 3 to 85 mg/m^2 Regimens: QW, twice weekly or QoD×3 (Wks 1 and 3) and twice weekly (Wks 2 and 4) 21-or 28-day cycles	Schedule 1 to 6: Mostly in days 1, 2, 3, 7 and 15 of cycle 1. Day 15-17 of cycle 2 and 3. Schedule 7: Day 1 of cycles 1 to 3. Schedule 8: Days 1 and 8 or cycle 1. Day 8 of cycle 2 and 3.
KCP-330-003 Phase 1b Pts with metastatic, locally advanced, unresectable, or locally recurrent soft tissue or bone sarcoma (N = 54)	Phase I Trial to Assess the Effects of Food and Formulation on PK of KPT-330 in Patients with Sarcoma	Selinexor Dose Regimen: 30 or 50 mg/m^2 or 60 mg twice weekly (4-wk cycles) Formulations: capsules, tablets (both first and second generation), and a liquid suspension (3 mg/mL). Arms 1 and 2: Evaluated formulation (capsule and tablet) and food effect. Arms 4, 5 and 6: Compared 2nd generation tablet and suspension to 1st generation tablet.	Arms 1 and 2: Weeks 1-4 of Cycle 1 at pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 18 (only for hospitalized patients) and 24 hr post-dose. Arms 4, 5 and 6: Day 1 of Weeks 1-3 of Cycle 1 at pre-dose and 0.167, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 18 (only for hospitalized patients), 24 and 48 hr post-dose.
KCP-330-008 SOPRA Phase 2 Pts with Relapsed or Refractory Acute	A Randomized, Open Label, Phase 2 Study of the Selective Inhibitor of Nuclear Export (Sine) Selinexor (KPT-330) Versus Specified Physician's Choice in Patients ≥ 60 Years	Selinexor Dose Regimen: 60 mg fixed dose or 55 mg/m^2 twice weekly, 4-wk cycle	Cycle 1: Day 1 of weeks 1 to 4. Cycles 2 to 5: Day 1 and Day 15. Cycle >=6: Day 1.

Myeloid Leukemia (N=213)	Old with Relapsed or Refractory Acute Myeloid Leukemia (AML) Who Are Ineligible for Intensive Chemotherapy and/or Transplantation	Control arm: One of the following: • BSC including blood product transfusions, antimicrobials, & GF • BSC + low dose AraC • BSC + hypomethylating agent	
KCP-330-009 SADAL Phase 2b Pts with RR DLBCL (N=220)	Selinexor (KPT-330) in Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma (DLBCL)	Low dose: Selinexor 60 mg, twice-weekly, 4-week cycle. High dose: Selinexor 100 mg, twice-weekly, 4-week cycle.	Cycle 1: Day 1 of weeks 1 to 4. Cycle 2: Day 1.
KCP-330-010 SIRRT Phase 2 Pts with initial or RR RT (N = 26)	Selinexor in Initial or Relapsed/Refractory Richter's Transformation (SIRRT)	Selinexor 60 mg twice weekly, 4-wk cycle	Cycle 1: Day 1 of weeks 1 to 3. Cycles 2 to 5: Day 1 and Day 15. Cycle > 6: Day 1.
KCP-330-012 STORM Phase 2b Part 1: Pts with penta refractory MM (N = 79) Part 2: Pts with quad- or penta refractory MM (N = 123)	A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) Plus Low--Dose Dexamethasone (Sd) in Patients with Multiple Myeloma Exposed to Bortezomib, Carfilzomib, Lenalidomide and Pomalidomide and Refractory to an IMiD and a Proteasome Inhibitor	Part 1: Selinexor 80 mg + dexamethasone 20 mg twice weekly (Days 1 and 3 for Wks 1 to 4), 4-wk cycles. Part 2: Selinexor 80 mg + dexamethasone 20 mg twice weekly (Days 1 and 3 for Wks 1 to 3), 4-wk cycles	PK was evaluated in Part 1 only. Cycle 1: Day 1 (predose, 1, 2, 4, hr postdose), Day 8 and 15 (predose, 1 hr post dose) Cycle 2: Day 1 (predose, 1, 2, 4, hr postdose),

Table 3 Summary of the Number of PK Samples and Exclusions

# of PK samples or Reason of exclusion	KCP-330-001	KCP-330-002	KCP-330-003	KCP-330-008	KCP-330-009	KCP-330-010	KCP-330-012	Total
All PK samples	**1978**	**1036**	**1367**	**2724**	**2547**	**237**	**799**	**10688**
Excluded in the final model (M4)								
Pre-dose samples	128	58	29	171	0	27	78	491
Incomplete PK sampling time	19	14	49	201	0	16	69	368
TAD > 200 hr	4	6	6	60	71	10	38	195
Incomplete dosing time	0	26	0	54	0	4	13	97
Above LLOQ samples collected between TAD 100 and 200 hr	0	0	0	12	39	0	0	51
BLQ samples collected between TAD 1 to24 hr	4	1	7	21	15	0	3	51
Duplicated samples	0	8	0	9	0	0	13	30
|CWRES| >5	0	0	1	2	3	0	0	6
N (%), M4 Method	**1823 (92.2%)**	**923 (89.1%)**	**1275 (93.3%)**	**2194 (80.5%)**	**2419 (95%)**	**180 (75.9%)**	**585 (73.2%)**	**9399 (87.9%)**
BLQ excluded in M1 method	214	105	138	693	760	37	133	2080
N(%), M1 Method	**1609 (81.3%)**	**818 (79%)**	**1137 (83.2%)**	**1501 (55.1%)**	**1659 (65.1%)**	**143 (60.3%)**	**452 (56.6%)**	**7319 (68.5%)**

Source: script\ 201901010-pk-summary-exploratory-v6.r
Abbreviations: TAD= time after last dose; BLQ= below the limit of quantification; LLOQ = lower limit of quantification ; CWRES= conditional weighted residuals.

Covariates distribution

Table 4 Summary of Continuous Covariates

Study	KCP-330-001	KCP-330-002	KCP-330-003	KCP-330-008	KCP-330-009	KCP-330-010	KCP-330-012	Total
N patient	131	59	37	200	261	26	79	793
Dose (mg)	55 (4 to 175)	25 (6 to 125)	60 (45 to 65)	60 (20 to 120)	60 (60 to 120)	60 (60 to 60)	80 (80 to 80)	60 (4 to 175)
Age (yr)	66 (24 to 89)	62 (31 to 76)	55 (18 to 80)	73 (60 to 94)	66 (18 to 91)	68 (41 to 79)	63 (34 to 78)	68 (18 to 94)
Weight (kg)	73 (38.6 to 144.7)	74.8 (36.5 to 129.4)	74 (45 to 132.1)	76 (43.4 to 134)	75 (45 to 157.9)	74.4 (47.3 to 115)	73.2 (39.3 to 168.5)	74.9 (36.5 to 168.5)
BMI (kg/m2)	25.4 (15.4 to 47.8)	25.5 (10.6 to 51.4)	27.2 (18.3 to 49.1)	26.2 (16.6 to 46.9)	26.1 (17 to 48.2)	25.1 (18.8 to 34.4)	26.4 (17.5 to 49.1)	25.9 (10.6 to 51.4)
BSA (m2)	1.8 (1.1 to 2.6)	1.9 (1.4 to 2.5)	1.8 (1.4 to 2.5)	1.9 (1.4 to 2.5)	1.9 (1.4 to 2.7)	1.9 (1.4 to 2.4)	1.9 (1.3 to 2.8)	1.9 (1.1 to 2.8)
ALB (g/L)	37 (21 to 65)	38 (19 to 47)	41 (28 to 50)	37.7 (22 to 49)	40 (21.5 to 53)	36.5 (24 to 44)	35 (19 to 46)	38 (19 to 65)
ALP (IU/L)	80.2 (26.1 to 779.6)	116 (48 to 505)	79.2 (50.1 to 246.5)	78.2 (43.1 to 732.5)	94 (31 to 561)	93.2 (45.1 to 590.2)	63.1 (30.1 to 539.1)	85 (26.1 to 779.6)
ALT (IU/L)	24 (1 to 192.4)	24 (6 to 132)	16 (5 to 86.2)	20 (6 to 135.3)	20 (4 to 267)	20.7 (7 to 137.3)	18 (6 to 67.1)	20 (1 to 267)
AST (IU/L)	24 (4 to 169.3)	29 (11 to 120)	18 (9 to 65.1)	21 (3 to 122.2)	24 (9 to 164)	25.4 (11 to 151.3)	22 (8 to 100.2)	23 (3 to 169.3)
BILI (mg/dL)	0.5 (0.1 to 6)	0.41 (0.1 to 3.74)	0.4 (0.18 to 0.88)	0.5 (0.12 to 3.2)	0.409 (0.088 to 5.1)	0.605 (0.3 to 2.8)	0.4 (0.2 to 1.6)	0.474 (0.088 to 6)
CRCL (mL/min)	77 (23.8 to 217.3)	94.8 (44.8 to 159.3)	99.5 (42.3 to 295.3)	72.9 (27.8 to 185.7)	78.2 (21.6 to 263.7)	71.4 (39.2 to 133.9)	68.9 (20 to 240.4)	77.7 (20 to 295.3)

Source: script\ 201901010-pk-summary-exploratory-v6.r
Note: Continuous values are reported as median (range).
Abbreviations: WT= body weight, BMI= body mass index, BSA= body surface area, ALB= serum albumin, ALP= alkaline phosphatase, ALT= serum alanine aminotransferase, AST= serum aspartate aminotransferase, BILI= total bilirubin, CRCL= creatinine clearance.

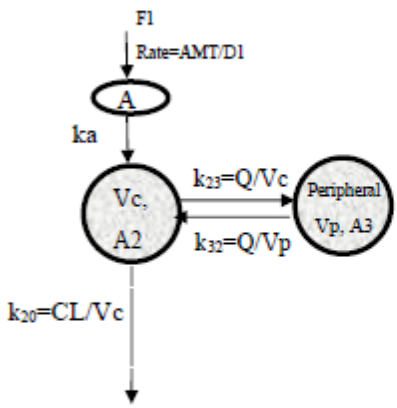
Table 5 Summary of the Number of Patients for Categorical Covariates

Study	KCP-330-001	KCP-330-002	KCP-330-003	KCP-330-008	KCP-330-009	KCP-330-010	KCP-330-012	Total
N patient	131	59	37	200	261	26	79	793
Sex (M/F)	76/55	35/24	17/20	122/78	163/98	17/9	37/42	467/326
Race (U/W/B/A/O)	2/114/10/4/1	0/54/4/1/0	1/29/2/5/0	4/174/7/2/13	15/204/8/14/20	0/26/0/0/0	0/62/14/0/3	22/663/45/26/37
Disease (haematological -Non-DLBCL/Solid/DLBCL)	131/0/0	0/59/0	0/37/0	200/0/0	0/0/261	26/0/0	79/0/0	436/96/261
ECOG (Missing/0/1/2/3)	0/33/92/6/0	0/14/45/0/0	0/18/19/0/0	5/54/111/30/0	1/99/128/32/1	1/7/13/5/0	6/15/49/9/0	13/240/457/82/1
FORM (Capsule/Tablet)	129/2	59/0	0/37	0/200	0/261	0/26	0/79	188/605
RI (Missing/Normal/Mild/Moderate/Severe)	1/38/62/26/4	0/34/18/7/0	0/22/12/3/0	0/62/80/54/3	1/97/95/66/2	0/6/13/7/0	0/24/29/22/4	2/283/309/185/13
HI (Missing/Normal/Mild/Moderate/Severe)	0/106/23/1/1	0/41/15/2/1	0/34/3/0/0	0/176/23/1/0	5/215/37/3/1	0/19/4/3/0	0/65/14/0/0	5/656/119/10/3
CYP3A4 inhibitor (None/weak/moderate/strong)*	94/0/32/5	56/0/2/1	35/0/2/0	107/0/76/17	154/47/52/8	21/0/5/0	75/0/2/2	542/47/171/33
CYP3A4 inducer (None/ weak/moderate/strong)*	131/0/0/0	59/0/0/0	37/0/0/0	199/0/0/1	116/142/1/2	26/0/0/0	78/0/0/1	646/142/1/4
CYP2D6 inhibitor (None/weak/strong)*	129/0/2	57/0/2	36/0/1	199/0/1	218/38/5	26/0/0	76/0/3	741/38/14
CYP2C8 inhibitor (None/ weak/ strong)*	130/0/1	59/0/0	37/0/0	194/0/6	257/3/1	26/0/0	79/0/0	782/3/8
Dexamethasone (No/Yes)*	75/56	38/21	9/28	108/92	153/108	16/10	0/79	399/394
PPI (No/Yes)	131/0	59/0	37/0	98/102	115/146	14/12	38/41	492/301
H2 blockers (No/Yes)	131/0	59/0	37/0	175/25	247/14	22/4	62/17	733/60

Source: script\ 201901010-pk-summary-exploratory-v6.r
Note: * Concomitant medications were counted for the strongest level of each patient.
Race abbreviation: U=unknown; W=white; B=Black; A=Asian; O=others.
Renal impairment (RI): Normal = CrCL >= 90 mL/min; Mild= CrCL 60 - < 90 mL/min; Moderate= CrCL 30 - < 60 mL/min; Severe= CrCL 15 - < 30 mL/min:

Final population PK model

Figure 4 Two-compartmental PK Model with Zero-order Release and First-order Absorption



AMT = dose amount given

F_1 = bioavailability of selinexor tablet/capsule

Rate = zero-order drug release rate

D1 = duration of zero-order drug release

Ka = first-order absorption rate

K_{20} = rate constant for the linear elimination from central compartment

K_{23} = rate constant from central to peripheral compartment

K_{32} = rate constant from peripheral to central compartment

CL = linear elimination clearance

Q =distribution clearance

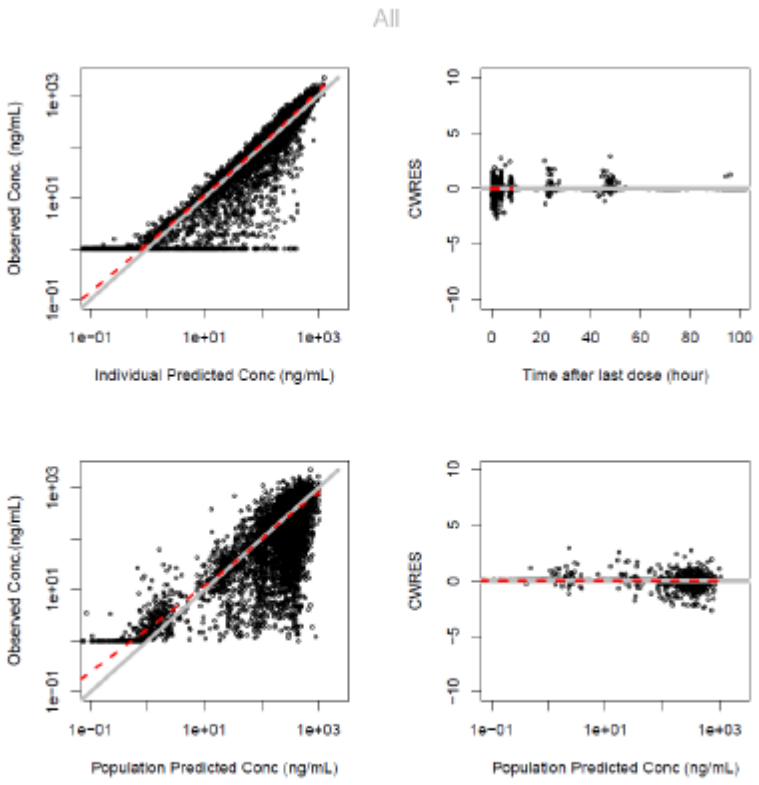
V_c = central volume

V_p = peripheral volume

Table 9 Final Model Parameter Estimates for Selinexor PK

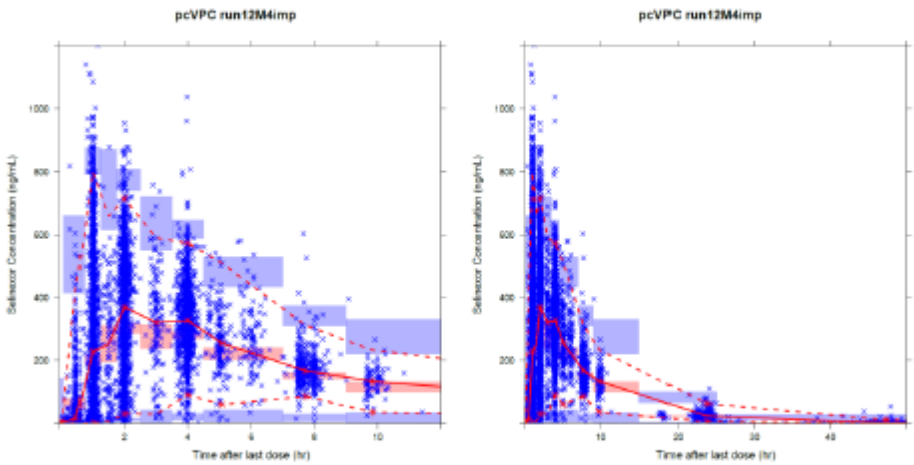
Parameters	Symbol	Estimate	RSE (%)	Bootstrap Median [2.5 to 97.5%ile]
CL/F (L/hr)	Θ_1	18.6	1.76	18.5 [17.9, 19.2]
Vc/F (L)	Θ_2	113	1.86	113 [109, 116]
Q/F (L/hr)	Θ_3	3.73	14	3.73 [2.92, 4.64]
Vp/F (L)	Θ_4	20.3	8.78	20.8 [17.3, 25.1]
Ka (1/hr)	Θ_5	2.27	7.2	2.05 [1.65, 2.69]
D1 (hr)	Θ_6	1.1	3.65	1.12 [1.02, 1.22]
WT-CL/F	Θ_9	0.577	9.58	0.575 [0.454, 0.705]
SEXF-CL/F	Θ_{10}	-0.0882	29.3	-0.0844 [-0.136, -0.0323]
WT-Vc/F	Θ_{11}	0.957	5.37	0.95 [0.842, 1.05]
Random effects				
CL/F	$\omega^2_{1,1}$	0.0383	11.6	0.0368 [0.0264, 0.05]
Vc/F x CL/F	$\omega^2_{1,2}$	0.0135	30	0.0115 [0.00149, 0.0219]
Vc/F	$\omega^2_{2,2}$	0.0354	18.2	0.0292 [0.0151, 0.0447]
Ka	$\omega^2_{3,3}$	1.94	9.59	1.73 [1.02, 2.53]
Ka x D1	$\omega^2_{3,4}$	-0.376	15.5	-0.412 [-0.542, -0.278]
D1	$\omega^2_{4,4}$	0.387	12.6	0.347 [0.26, 0.444]
Inter-Occasion variability				
Ka	$\omega^2_{5,5}$	3.7	6.68	3.5 [2.69, 4.57]
Residual error				
Proportional	Θ_7	0.441	1.19	0.443 [0.427, 0.455]
Additive (ng/mL)	Θ_8	0.744	1.8	0.734 [0.145, 1.15]

Figure 6 GOF Plots for the Final Model



Source: script/20191010-final-model-review-model12M4imp.r
Notes: Dots are individual data points, and dashed red lines are smoothed LOESS lines. In the two plots in the left column row, solid lines are lines of identity, while in the two plots in the right column, solid horizontal lines show the zero value.
Abbreviations: CWRES=conditional weighted residuals.

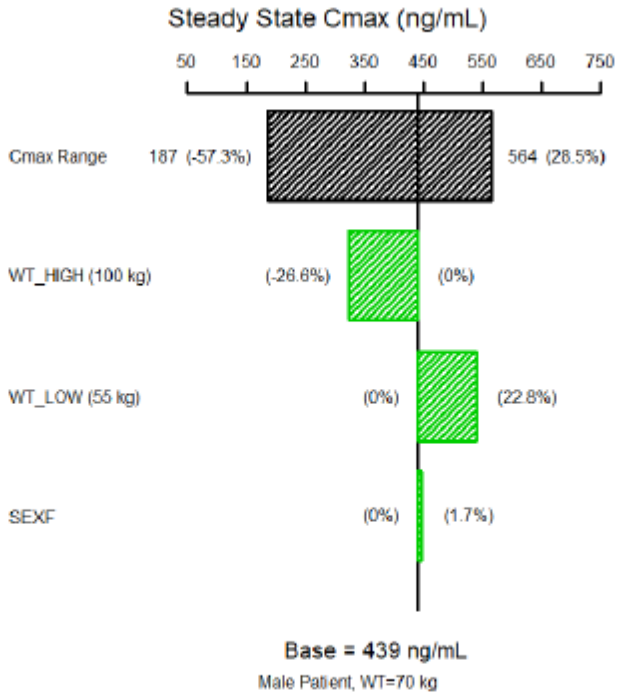
Figure 8 Prediction-Corrected VPC of the Final Model Over Hours 0-12 (left) and 0-50 (right)



Source: script/20191010-final-model-review-model12M4imp.r
Notes: Blue dots are observed data points; red solid line is the observed median; red dashed lines are observed p5 and p95. The pink area is the 95% prediction interval (PI) of the simulated median, and purple areas are the 95% PI of the simulated p5 and p95.

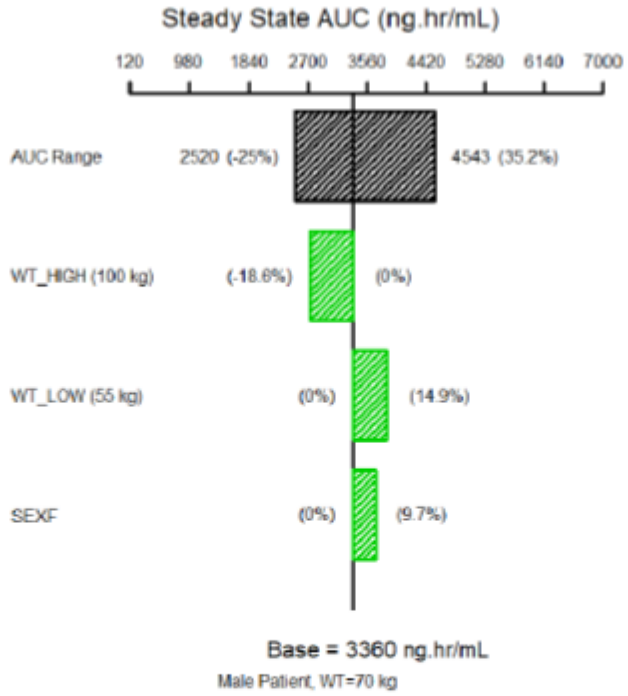
Impact of covariates on PK exposure

Figure 9 **Impact of Covariates on Steady State Cmax**



Source: script/20191010 final pk model simulations model12M4imp.r
Notes: Black bar represents 5th to 95th percentile of the exposure calculated using Empirical Bayes Estimates of the population at week 4 for a dose regimen of 60 mg BIW (dose given on Day 1 and Day 3 of a week). The impact of a covariate on the exposure was calculated using the parameter(s) incorporating the isolated effect of that covariate, with other unaffected parameters fixed to the typical values (estimated for a male patient with baseline body weight

Figure 10 Impact of Covariates on Steady State AUC



Source: script/20191010 final pk model simulations model12M4imp.r
Notes: Black bar represents 5th to 95th percentile of the exposure calculated using Empirical Bayes Estimates of the population at week 4 for a dose regimen of 60 mg BIW (dose given on Day 1 and Day 3 of a week). The impact of a covariate on the exposure was calculated using the parameter(s) incorporating the isolated effect of that covariate, with other unaffected parameters fixed to the typical values (estimated for a male patient with baseline body weight of 70 kg). Baseline body weight were evaluated at 10th to 90th percentile of the population. SEXF is covariate effect of female gender.

Other covariates evaluated, including dose, formulation, patient type, ECOG status, baseline labs and concomitant medications (CYP3A4 inhibitors/inducers, CYP2D6 inhibitors, CYP2C8 inhibitors, dexamethasone, PPIs and H2 blockers), had no impact on the selinexor PK. The exposure of selinexor is dose proportional in the dose range from 4 to 175 mg. Patients with DLBCL had similar exposure level to patients with Non-DLBCL haematological malignancies or solid tumour.

Population PK model in patients with multiple myeloma

Dataset

Forty (40) selinexor PK samples were collected from 8 patients with relapsed or refractory multiple myeloma in study BOSTON. The PK results of study BOSTON were combined with the dataset used for the previous analysis [1] to form an updated analysis dataset. The consolidated dataset included 9439 selinexor PK observations from 801 patients with acute myeloid leukemia (AML), diffuse large B-cell lymphoma (DLBCL), MM, other hematologic cancers or other solid cancers.

Table 1 Summary of Continuous Baseline Covariates by Study

Study	KCP-330-001	KCP-330-002	KCP-330-003	SOPRA (KCP-330-008)	SADAL (KCP-330-009)	SIRRT (KCP-330-010)	STORM (KCP-330-012)	BOSTON (KCP-330-023)	Total
N patient	131	59	37	200	261	26	79	8	801
Dose (mg)	55 (4 to 175)	25 (6 to 125)	60 (45 to 65)	60 (20 to 120)	60 (60 to 120)	60 (60 to 60)	80 (80 to 80)	100 (100 to 100)	60 (4 to 175)
Age (yr)	66 (24 to 89)	62 (31 to 76)	55 (18 to 80)	73 (60 to 94)	66 (18 to 91)	68 (41 to 79)	63 (34 to 78)	51 (40 to 81)	68 (18 to 94)
Weight (kg)	73 (38.6 to 144.7)	74.8 (36.5 to 129.4)	74 (45 to 132.1)	76 (43.4 to 134)	75 (45 to 157.9)	74.4 (47.3 to 115)	73.2 (39.3 to 168.5)	79 (70.3 to 92.9)	75 (36.5 to 168.5)
BMI (kg/m^2)	25.4 (15.4 to 47.8)	25.5 (10.6 to 51.4)	27.2 (18.3 to 49.1)	26.2 (16.6 to 46.9)	26.1 (17 to 48.2)	25.1 (18.8 to 34.4)	26.4 (17.5 to 49.1)	26 (20.9 to 32.5)	25.9 (10.6 to 51.4)
BSA (m^2)	1.85 (1.05 to 2.61)	1.89 (1.41 to 2.50)	1.80 (1.41 to 2.45)	1.88 (1.35 to 2.51)	1.86 (1.38 to 2.68)	1.92 (1.45 to 2.36)	1.86 (1.29 to 2.82)	1.91 (1.79 to 2.08)	1.86 (1.05 to 2.82)
ALB (g/L)	37 (21 to 65)	38 (19 to 47)	41 (28 to 50)	37.7 (22 to 49)	40 (21.5 to 53)	36.5 (24 to 44)	35 (19 to 46)	38 (31 to 42)	38 (19 to 65)
ALP (IU/L)	80.2 (26.1 to 779.6)	116 (48 to 505)	79.2 (50.1 to 246.5)	78.2 (43.1 to 732.5)	94 (31 to 561)	93.2 (45.1 to 590.2)	63.1 (30.1 to 539.1)	71.5 (51 to 78)	84.2 (26.1 to 779.6)
ALT (IU/L)	24 (1 to 192.4)	24 (6 to 132)	16 (5 to 86.2)	20 (6 to 135.3)	20 (4 to 267)	20.7 (7 to 137.3)	18 (6 to 67.1)	17.5 (12 to 58)	20 (1 to 267)
AST (IU/L)	24 (4 to 169.3)	29 (11 to 120)	18 (9 to 65.1)	21 (3 to 122.2)	24 (9 to 164)	25.4 (11 to 151.3)	22 (8 to 100.2)	22.5 (12 to 43)	23 (3 to 169.3)
BILI (mg/dL)	0.5 (0.1 to 6)	0.41 (0.1 to 3.74)	0.4 (0.18 to 0.88)	0.5 (0.12 to 3.2)	0.409 (0.088 to 5.1)	0.605 (0.3 to 2.8)	0.4 (0.2 to 1.6)	0.35 (0.2 to 0.6)	0.47 (0.088 to 6)
CRCL (mL/min)	77 (23.8 to 217.3)	94.8 (44.8 to 159.3)	99.5 (42.3 to 295.3)	72.9 (27.8 to 185.7)	78.2 (21.6 to 263.7)	71.4 (39.2 to 133.9)	68.9 (20 to 240.4)	106.1 (32.8 to 119.1)	78 (20 to 295.3)

Source: script\ 20200317-pk-summary-exploratory-v3.r
Note: Continuous values are reported as median (range).
Abbreviations: WT= body weight, BMI= body mass index, BSA= body surface area, ALB= serum albumin, ALP= alkaline phosphatase, ALT= serum alanine aminotransferase, AST= serum aspartate aminotransferase, BILI= total bilirubin, CRCL= creatinine clearance.

Covariates distribution

Table 1 Summary of Continuous Baseline Covariates by Study

Study	KCP-330-001	KCP-330-002	KCP-330-003	SOPRA (KCP-330-008)	SADAL (KCP-330-009)	SIRRT (KCP-330-010)	STORM (KCP-330-012)	BOSTON (KCP-330-023)	Total
N patient	131	59	37	200	261	26	79	8	801
Dose (mg)	55 (4 to 175)	25 (6 to 125)	60 (45 to 65)	60 (20 to 120)	60 (60 to 120)	60 (60 to 60)	80 (80 to 80)	100 (100 to 100)	60 (4 to 175)
Age (yr)	66 (24 to 89)	62 (31 to 76)	55 (18 to 80)	73 (60 to 94)	66 (18 to 91)	68 (41 to 79)	63 (34 to 78)	51 (40 to 81)	68 (18 to 94)
Weight (kg)	73 (38.6 to 144.7)	74.8 (36.5 to 129.4)	74 (45 to 132.1)	76 (43.4 to 134)	75 (45 to 157.9)	74.4 (47.3 to 115)	73.2 (39.3 to 168.5)	79 (70.3 to 92.9)	75 (36.5 to 168.5)
BMI (kg/m^2)	25.4 (15.4 to 47.8)	25.5 (10.6 to 51.4)	27.2 (18.3 to 49.1)	26.2 (16.6 to 46.9)	26.1 (17 to 48.2)	25.1 (18.8 to 34.4)	26.4 (17.5 to 49.1)	26 (20.9 to 32.5)	25.9 (10.6 to 51.4)
BSA (m^2)	1.85 (1.05 to 2.61)	1.89 (1.41 to 2.50)	1.80 (1.41 to 2.45)	1.88 (1.35 to 2.51)	1.86 (1.38 to 2.68)	1.92 (1.45 to 2.36)	1.86 (1.29 to 2.82)	1.91 (1.79 to 2.08)	1.86 (1.05 to 2.82)
ALB (g/L)	37 (21 to 65)	38 (19 to 47)	41 (28 to 50)	37.7 (22 to 49)	40 (21.5 to 53)	36.5 (24 to 44)	35 (19 to 46)	38 (31 to 42)	38 (19 to 65)
ALP (IU/L)	80.2 (26.1 to 779.6)	116 (48 to 505)	79.2 (50.1 to 246.5)	78.2 (43.1 to 732.5)	94 (31 to 561)	93.2 (45.1 to 590.2)	63.1 (30.1 to 539.1)	71.5 (51 to 78)	84.2 (26.1 to 779.6)
ALT (IU/L)	24 (1 to 192.4)	24 (6 to 132)	16 (5 to 86.2)	20 (6 to 135.3)	20 (4 to 267)	20.7 (7 to 137.3)	18 (6 to 67.1)	17.5 (12 to 58)	20 (1 to 267)
AST (IU/L)	24 (4 to 169.3)	29 (11 to 120)	18 (9 to 65.1)	21 (3 to 122.2)	24 (9 to 164)	25.4 (11 to 151.3)	22 (8 to 100.2)	22.5 (12 to 43)	23 (3 to 169.3)
BILI (mg/dL)	0.5 (0.1 to 6)	0.41 (0.1 to 3.74)	0.4 (0.18 to 0.88)	0.5 (0.12 to 3.2)	0.409 (0.088 to 5.1)	0.605 (0.3 to 2.8)	0.4 (0.2 to 1.6)	0.35 (0.2 to 0.6)	0.47 (0.088 to 6)
CRCL (mL/min)	77 (23.8 to 217.3)	94.8 (44.8 to 159.3)	99.5 (42.3 to 295.3)	72.9 (27.8 to 185.7)	78.2 (21.6 to 263.7)	71.4 (39.2 to 133.9)	68.9 (20 to 240.4)	106.1 (32.8 to 119.1)	78 (20 to 295.3)

Source: script\ 20200317-pk-summary-exploratory-v3.r
Note: Continuous values are reported as median (range).
Abbreviations: WT= body weight, BMI= body mass index, BSA= body surface area, ALB= serum albumin, ALP= alkaline phosphatase, ALT= serum alanine aminotransferase, AST= serum aspartate aminotransferase, BILI= total bilirubin, CRCL= creatinine clearance.

Table 2 Summary of the Number of Patients for Categorical Baseline Covariates by Study

Study	KCP-330-001	KCP-330-002	KCP-330-003	SOPRA (KCP-330-008)	SADAL (KCP-330-009)	SIRRT (KCP-330-010)	STORM (KCP-330-012)	BOSTON (KCP-330-023)	Total
N patient	131	59	37	200	261	26	79	8	801
Sex (M/F)	76/55	35/24	17/20	122/78	163/98	17/9	37/42	7/1	474/327
Race (U/W/B/A/O)	2/114/10/4/1	0/54/4/1/0	1/29/2/5/0	4/174/7/2/13	15/204/8/14/20	0/26/0/0/0	0/62/14/0/3	0/5/2/1/0	22/668/47/27/37
Tumor type (AML/DLBCL/MM/Other Hematologic Cancer/Other Solid Cancer)	54/20/26/31/0	0/0/0/0/59	0/0/0/0/37	200/0/0/0/0	0/261/0/0/0	0/0/0/26/0	0/0/79/0/0	0/0/8/0/0	254/281/113/57/96
ECOG (Missing/0/1/2/3)	0/33/92/6/0	0/14/45/0/0	0/18/19/0/0	5/54/111/30/0	1/99/128/32/1	1/7/13/5/0	6/15/49/9/0	0/4/4/0/0	13/244/461/82/1
Formulation (Capsule/Tablet)	129/2	59/0	0/37	0/200	0/261	0/26	0/79	0/8	188/613
Renal impairment (RI) (Missing/Normal/Mild/Moderate/Severe)	1/38/62/26/4	0/34/18/7/0	0/22/12/3/0	1/62/80/54/3	1/97/95/66/2	0/6/13/7/0	0/24/29/22/4	0/5/1/2/0	3/288/310/187/13
Hepatic impairment (HI) (Missing/Normal/Mild/Moderate/Severe)	0/106/23/1/1	0/41/15/2/1	0/34/3/0/0	0/176/23/1/0	5/215/37/3/1	0/19/4/3/0	0/65/14/0/0	0/8/0/0/0	5/664/119/10/3
CYP3A4 inhibitor (None/weak/moderate/strong)*	94/0/32/5	56/0/2/1	35/0/2/0	105/0/77/18	154/47/52/8	21/0/5/0	75/0/2/2	5/1/2/0	545/48/174/34
CYP3A4 inducer (None/ weak/moderate/strong)*	131/0/0/0	59/0/0/0	37/0/0/0	199/0/0/1	116/142/1/2	26/0/0/0	78/0/0/1	0/8/0/0	646/150/1/4
CYP2D6 inhibitor (None/weak/strong)*	129/0/2	57/0/2	36/0/1	199/0/1	218/38/5	26/0/0	76/0/3	8/0/0	749/38/14
CYP2C8 inhibitor (None/ weak/ strong)*	130/0/1	59/0/0	37/0/0	194/0/6	257/3/1	26/0/0	79/0/0	8/0/0	790/3/8
Dexamethasone (No/Yes)	75/56	38/21	9/28	108/92	153/108	16/10	0/79	0/8	399/402
Proton pump inhibitor (PPI, No/Yes)	131/0	59/0	37/0	98/102	115/146	14/12	38/41	5/3	497/304
H2 blockers (No/Yes)	131/0	59/0	37/0	175/25	247/14	22/4	62/17	7/1	740/61

Source: script\ 20200317-pk-summary-exploratory-v3.r

Note: * Concomitant medications were counted for the strongest level of each patient.

Race abbreviation: U=unknown; W=white; B=Black; A=Asian; O=others.

Renal impairment (RI): Normal = CrCL >= 90 mL/min; Mild= CrCL 60 - < 90 mL/min; Moderate= CrCL 30 - < 60 mL/min; Severe= CrCL 15 - < 30 mL/min;

Hepatic impairment (HI) : Normal = AST and BILI <= ULN; Mild = BILI between 1 and 1.5 times the ULN, regardless of AST; Mild = BILI <= ULN and AST > ULN; Moderate = BIL between 1.5 and 3.0 times the ULN; Severe = BIL > 3 times the ULN.

Cancer types: AML= acute myeloid leukemia; DLBCL= diffuse large B-cell lymphoma; MM = multiple myeloma.

Final population PK model

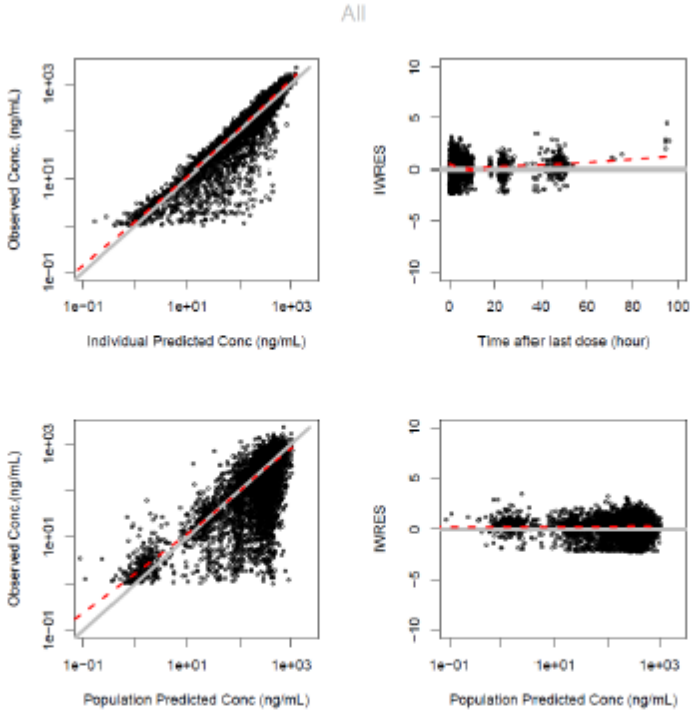
Table 3 Final Model Parameter Estimates for Selinexor PK

		Previous model [1]		Updated Final Model	
Parameters	**Symbol**	**Estimate**	**RSE (%)**	**Estimate**	**RSE (%)**
CL/F (L/hr)	Θ_1	18.6	1.76	18.5	1.76
Vc/F (L)	Θ_2	113	1.86	113	1.81
Q/F (L/hr)	Θ_3	3.73	14	3.69	14.3
Vp/F (L)	Θ_4	20.3	8.78	20.3	9.04
Ka (1/hr)	Θ_5	2.27	7.2	2.30	15.2
D1 (hr)	Θ_6	1.1	3.65	1.13	4.47
WT-CL/F	Θ_9	0.577	9.58	0.578	9.65
SEXF-CL/F	Θ_{10}	-0.0882	29.3	-0.0847	29.9
WT-Vc/F	Θ_{11}	0.957	5.37	0.932	5.72
Random effects					
CL/F	$\omega^2_{1,1}$	0.0383	11.6	0.0361	11.1
Vc/F x CL/F	$\omega^2_{1,2}$	0.0135	30	0.0113	28.6
Vc/F	$\omega^2_{2,2}$	0.0354	18.2	0.0323	16.7
Ka	$\omega^2_{3,3}$	1.94	9.59	2.00	12.8
Ka x D1	$\omega^2_{3,4}$	-0.376	15.5	-0.376	15.1
D1	$\omega^2_{4,4}$	0.387	12.6	0.360	12.6
Inter-Occasion variability					
Ka	$\omega^2_{5,5}$	3.7	6.68	3.69	6.87
Residual error					
Proportional	Θ_7	0.441	1.19	0.442	1.2
Additive (ng/mL)	Θ_8	0.744	1.8	0.743	1.79

Source: script/ 20200330-final-model-review-model2.r

Abbreviations: F= bioavailability; CL/F=apparent clearance; Vc/F=apparent central volume of distribution; Q/F=apparent inter-compartmental clearance; V_p/F=apparent peripheral volume of distribution; Ka=absorption rate constant; D1=zero-order drug release duration; RSE=relative standard error; WT = body weight; SEXF=female sex.

Figure 3 GOF Plots of the Final Model (All studies)

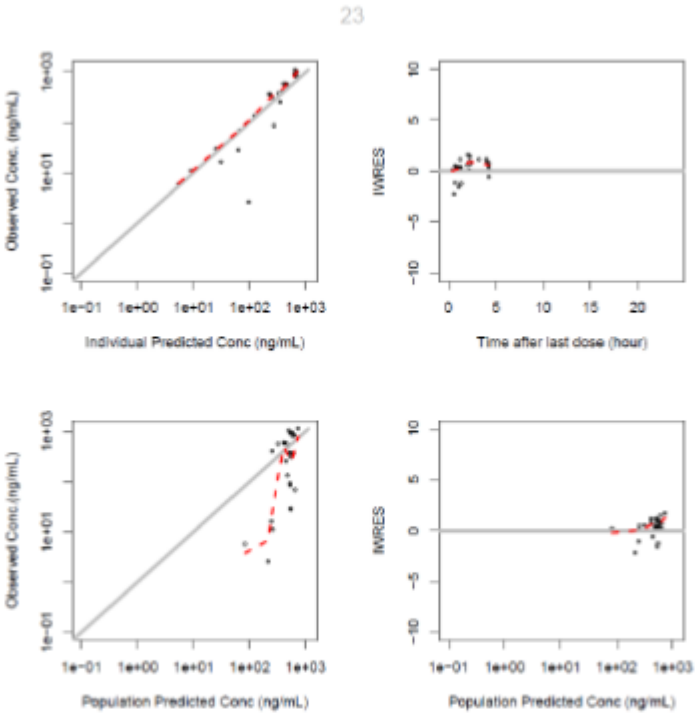


Source: script/ 20200330-final-model-review-model2.r

Notes: Dots are individual data points, and dashed red lines are smoothed LOWESS lines. In the two plots in the left column, solid lines are lines of identity, while in the two plots in the right column, solid horizontal lines show the zero value. PK observations with concentration below the LLOQ are not included in the GOF plots.

Abbreviations: IWRES= individual weighted residuals.

Figure 4 GOF Plots for the Final Model (Study BOSTON)



Source: script/ 20200330-final-model-review-model2.r

Notes: Dots are individual data points, and dashed red lines are smoothed LOWESS lines. In the two plots in the left column, solid lines are lines of identity, while in the two plots in the right column, solid horizontal lines show the zero value. PK observations with concentration below the LLOQ are not included in the GOF plots.

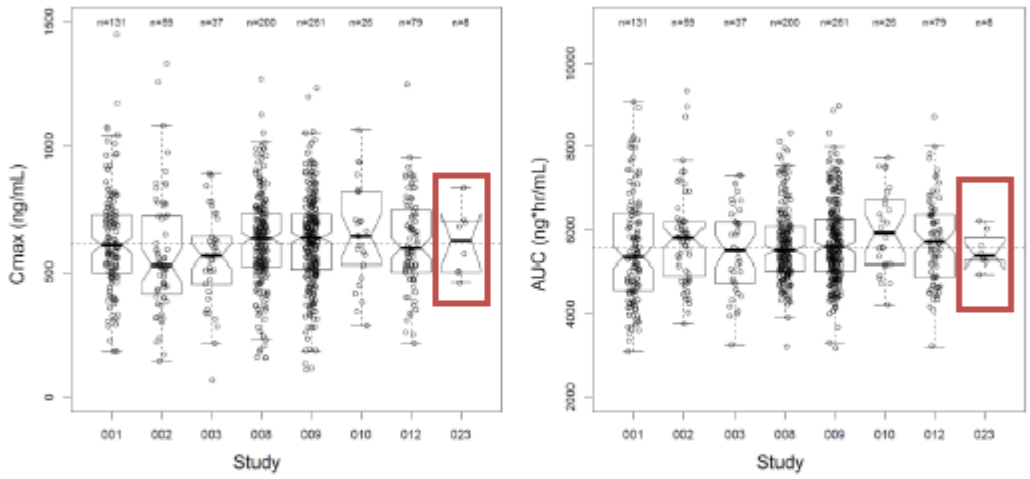
Abbreviations: IWRES= individual weighted residuals.

Model simulations

Steady state selinexor PK exposure were simulated using the Bayesian post-hoc PK parameters of each individual, where the impact of covariates and their correlation were accounted for. The simulation was done for the regimen of 100 mg QW.

Boxplots of PK exposure are illustrated in Figure 6 and Figure 7 by study and tumour type, respectively. Although the number of patients was limited, PK exposure of study BOSTON appear to be similar to other studies including study KCP-330-012 (also in patients with MM) and study KCP-330-009 (patients with DLBCL). Selinexor was co-administrated with bortezomib and dexamethasone in study BOSTON, while it was co-administrated with dexamethasone alone in study KCP-330-012. The addition of bortezomib appears to have no impact on the selinexor PK. Comparing the PK exposure in patients with different patient types, Cmax and AUC in patients with MM were similar to the values in patients with AML, DLBCL and other hematologic and solid tumour types (Figure 7).

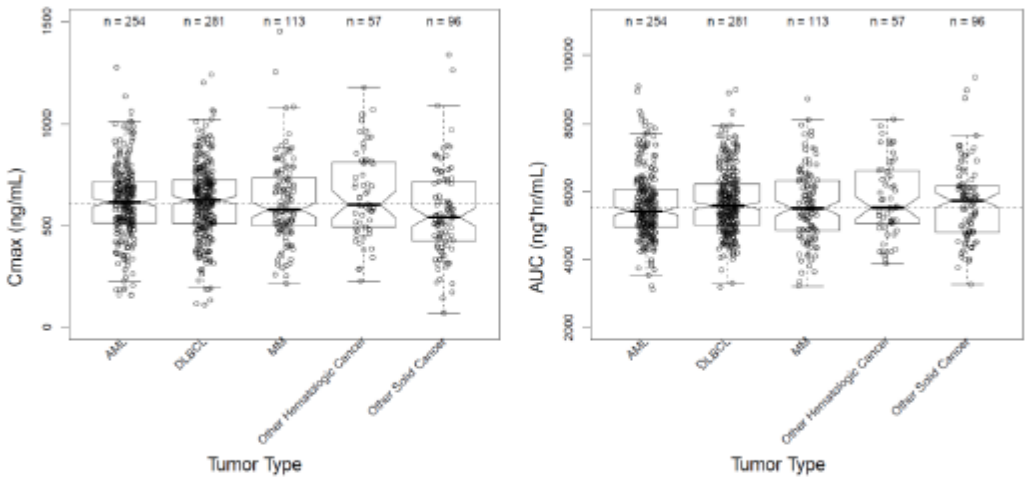
Figure 6 Boxplots of Simulated Steady State C_{max} or AUC with 100 mg Selinexor QW by Study



Source: script/20200330-final-pk-model-simulations-model2.r

Notes: circles – simulated individual PK exposure for 100 mg QW regimen at steady state. Boxplots show the median (solid bold line), the interquartile range (boxes), 1.5 times the interquartile range (whiskers). Points are jittered in the x-axis direction for clarity. Dashed horizonal line indicates median exposure of the overall population. Two patients with extreme AUC values are outside of the plotting range but are included in the interquartile analysis. Red box indicates the new study (study BOSTON). 001 = KCP-330-001; 002 = KCP-330-002; 003 = KCP-330-003; 008 = KCP-330-008; 009 = KCP-330-009; 010 = KCP-330-010; 012 = KCP-330-012; 023 = KCP-330-023.

Figure 7 Boxplots of Simulated Steady State C_{max} or AUC with 100 mg Selinexor QW by Tumor Types



Source: script/20200330-final-pk-model-simulations-model2.r

Notes: circles – simulated individual PK exposure for 100 mg QW regimen at steady state. Boxplots show the median (solid bold line), the interquartile range (boxes), 1.5 times the interquartile range (whiskers). Points are jittered in the x-axis direction for clarity. Dashed horizonal line indicates median exposure of the overall population. Two patients with extreme AUC values are outside of the plotting range but are included in the interquartile analysis.

Special populations

Hepatic impairment

To verify previous findings and to satisfy PMR 3657-3, the effect of hepatic impairment on selinexor PK was formally evaluated in a separate clinical trial.

Based on the second set of population PK analyses from pooled Phase 1 and 2 studies, the PK of selinexor was not substantially altered in patients with various degrees of hepatic impairment (based on National Cancer Institute organ dysfunction working group [NCI-ODWG] criteria) present either at baseline (N = 119 for mild, N = 10 for moderate, N = 3 for severe). The effect of liver function on clearance of selinexor was evaluated across patients with various liver function test values in these population PK analyses. No significant relationships were identified between PK parameters and baseline total bilirubin, AST, ALT, ALB, or hepatic impairment.

Taken together, the results demonstrated that selinexor clearance was not altered substantially as a function of the severity of liver impairment. Therefore, no dose adjustment is necessary in patients with mild, moderate, or severe hepatic impairment.

Renal impairment

Based on the concentrations of selinexor measured in urine (Study 003), renal clearance is a minor route of elimination for selinexor. Population PK analyses from patients with normal (N = 283), mild (N = 309), moderate (N = 185), or severe (N = 13), renal dysfunction were evaluated (mean [min, max] baseline CrCL = 77.7 [20, 295.3] mL/min) from Phase 1 and 2 studies were conducted. Baseline CrCL had no impact on the PK of selinexor. Therefore, mild, moderate, or severe renal impairment is not expected to alter selinexor PK, and no selinexor dose adjustments are required in patients with renal dysfunction.

Pharmacokinetic interaction studies

The effect of a strong CYP3A inhibitor on the PK of selinexor will be formally evaluated in Study KCP-330-017 (Study 017/STOMP) to verify the findings from population PK analyses and to satisfy post-marketing requirement (PMR) 3657-4.

Selinexor once weekly (QW) is not expected to alter exposures of other drugs and exposures to selinexor are unlikely to be affected by concomitant administrations of modulators of major CYP enzymes, including CYP3A4, based on in vitro drug-drug interaction (DDI) evaluations and population PK analysis that included more than 700 patients with PK data.

A thorough investigation for drug interaction potential was done by conducting a series of *in vitro* studies which included CYP phenotyping, UGT phenotyping, metabolic stability, substrate and inhibition assessment of metabolic transporters, and inhibition of major human CYP enzymes. The very low turnover in HLM and recombinant enzymes suggested selinexor is metabolically stable. The limited metabolism was catalyzed by CYP3A4 (and not the other CYP enzymes), UGTs and GSTs.

Selinexor is not a substrate for major metabolic hepatic, renal, and intestinal transporters breast cancer resistance protein (BCRP), permeability glycoprotein (P-gp), organic anion transporting polypeptide OATP1B1, OATP1B3, organic anion transporter OAT1, OAT3, organic cation transporter OCT1, OCT2, multidrug and toxin extrusion MATE1 and MATE2-K (Section 2.1.4). Selinexor did not inhibit metabolic solute carrier (SLC) transporters except for marginal inhibition of OATP1B1 and 1B3, which may not be clinically relevant. The potential for DDIs due to inhibition of major human CYPs (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5) is very low (all concentrations resulting in 50% of the maximum inhibition (IC50s) values for CYP inhibition >10 µM), including CYP3A4/5 IC50 of 24 µM and no demonstrable CYP induction is observed.

Although selinexor is metabolized by conjugation with GSH, co-administration with acetaminophen (paracetamol) at therapeutic dose was found not to affect the PK of selinexor. In a subset of patients

evaluated in Study 002 co-administration of acetaminophen at doses up to 1000 mg appeared to have no effect on the exposure of selinexor.

In the second population PK model, no significant relationships were identified between model parameters and concomitant administration of CYP3A4/2D6/2C8 modulators, dexamethasone, proton pump inhibitors, and H2 blockers.

Based on the metabolism and *in vitro* drug interaction profiles of selinexor and bortezomib, no drug-drug interaction between selinexor and bortezomib is expected. Exposure parameters (Cmax and AUC) of selinexor in patients in BOSTON who received combination dosing of selinexor, bortezomib and dexamethasone were shown to be similar to patients in selinexor monotherapy studies (MS-003) and confirm the lack of effect of bortezomib on the PK of selinexor.

Based on findings from in vitro studies and given that there have been no clinically significant DDIs reported in >3200 patients treated with selinexor alone or in combination as of this Type II variation, the overall risk for PK based DDIs with selinexor is considered to be low. Moreover, no DDIs have been reported in post-marketing studies to date.

2.3.3. Pharmacodynamics

Primary and secondary pharmacology

Exposure-QT analyses

No proarrhythmic effects of selinexor have been documented to date, and none of the new analyses as described below have raised concerns along these lines.

The concentration-QT modelling analyses included data for PK time-matched QTc from 85 patients from the two Phase 1 studies Study 001 and Study 003. No significant ($p>0.05$) relationship by dose levels was observed between QT interval corrected by Fridericia's formula (ΔQTcF) and selinexor concentrations. Linear mixed-effect modelling demonstrated a small positive slope such that a selinexor concentration of 1200 ng/mL (approximately 2-fold of the anticipated therapeutic concentration [Cmax] from the 100 mg dose) correlates with a potential mean ΔQTcF increase of 7.2 msec, with a 90% CI of <20 msec increase above baseline. Therefore, selinexor is not expected to cause clinically relevant QTc prolongation at the therapeutic dose concentrations of selinexor with ΔQTcF expected to remain within 20 msec of baseline. Additionally, none of the patients had a ΔQTcF of >60 msec in the PK population.

A categorical outlier analysis and an analysis of proarrhythmic AEs of the ECG intervals in Study 001 and Study 003 was also conducted. In addition, all patients with post-treatment QTcF ≥500 msec or QTcF >60 msec change from baseline were on concomitant medications known to prolong QT and many had electrolyte abnormalities. The majority of proarrhythmic AEs were at Grade 2 or less and were considered by investigators as not related to the study treatment. The results from all the analyses discussed above demonstrated that selinexor does not cause QT prolongation at exposures or doses well above therapeutic doses.

2.3.4. PK/PD modelling

Selinexor exposure-efficacy relationships in RRMM patients and exposure-safety relationships in patients with advanced hematologic malignancies were evaluated in the initial MAA.

Exposure-response efficacy analyses were conducted to evaluate the effect of exposure (AUC) and dose intensity on the measures of efficacy, including overall response rate (ORR), clinical benefit rate (CBR), best overall response (BOR), progression-free survival (PFS), and overall survival (OS), in patients with heavily pre-treated MM who received selinexor plus dexamethasone (Sd regimen) assuming that efficacy

responses were driven by selinexor. No discernible exposure-efficacy relationships were observed for patients who received 80 mg selinexor plus low-dose dexamethasone.

Exposure-safety logistic regression analyses were conducted for the five endpoints (thrombocytopenia, hyponatremia, and fatigue Grade ≥3 TEAEs as well as AEs leading to discontinuation or death). Both AUC and Cmax were used as exposure metrics in the analyses. Statistically significant trends for increases in ≥ Grade 3 events of hyponatremia, fatigue, and AEs leading to discontinuation were found through logistic regression modelling.

Exposure-response analyses were not conducted using data from the BOSTON study given the limited PK data obtained (8 patients and 40 samples) and given the availability of prior analyses and data (STORM study) to inform the expected efficacy and safety of selinexor and bortezomib combination therapy. Exposure-response relationships presented in the initial MAA are useful to inform the contribution of selinexor and dexamethasone when used in combination with bortezomib in BOSTON on applicable safety endpoints for patients with multiple myeloma.

2.3.5. Discussion on clinical pharmacology

The investigation into bortezomib instability in human plasma K_2EDTA indicates that bortezomib can be unstable in certain untreated human plasma K_2EDTA. The observed instability is dependent on unknown interactions in human plasma K_2EDTA. In some individual matrix lots, bortezomib was stable after 48 hours of storage at -20 ºC or -70 ºC. Pretreatment with formic acid is needed to stabilize bortezomib in K_2EDTA (stored at 5 ºC, -20 ºC or -70 ºC) or NaHeparin (stored at -20 ºC or -70 ºC) human plasma.

The clinical pharmacology properties of selinexor have been evaluated to fulfil the Specific Obligation of the Conditional Marketing Authorization on the use of selinexor in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy. An additional indication has been requested to support the use of selinexor in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma (MM) who have received at least 1 prior therapy, based on the global Phase 3 BOSTON (KCP-330-023) study. The proposed dosing regimen for the new indication is selinexor 100 mg QW PO, bortezomib 1.3 mg/m2 QW, and dexamethasone 20 mg BIW PO.

DLBCL and other cancer types

In order to support the positive opinion for the initial MAA, the Applicant applied a two-compartment model with sequential zero- and first-order absorption kinetics to data from 793 patients across 7 clinical studies. The final population PK parameters were precisely estimated, based on the relative standard error (<30%) and statistically significant, based on the 95% confidence interval (CI). However, the large inter-individual variability associated to ka (1.94) leads to an over-estimation of the inter-individual random effects, which translates into an over-prediction of the Cmax (Figures 6 and 8). The Applicant evaluated additional factors on ka, but none of them were statistically significant or led to clinically relevant differences in exposure. Final population PK model incorporates sex on CL/F, and body weight on CL/F and Vc/F and the final parameter estimates are in agreement with standard values reported in the literature. The impact of covariates on selinexor exposure of patients with DLBCL and other cancer types suggested no clinically relevant changes in terms of selinexor AUC.

Multiple myeloma

In order to support the indication of selinexor in patients with multiple myeloma (MM), the PK properties of selinexor were characterized based on the previously developed population PK model in patients with DLBCL and other cancer types. The Applicant has conducted the evaluation of experimental evidence gathered from study BOSTON to inform that neither the disease condition nor the combination with bortezomib are affecting the PK properties of selinexor. The lack of significant differences in the adequacy of the popPK predictions among the different study types demonstrated the validity of the experimental evidence considered to develop the population PK model. No significant differences were observed on CL/F and V/F between patients with MM from the STORM and BOSTON studies. At the same time, the pc-VPC is able to characterize the experimental evidence with good agreement, although the prediction interval covers the 5-95th percentiles (which should be done only when sparse data (KCP-330-023 study) is available).

2.3.6. Conclusions on clinical pharmacology

The characterization of the clinical pharmacology properties of Selinexor, regarding the indication of selinexor in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma (MM) who have received at least 1 prior therapy, is endorsed. The level of evidence provided is considered sufficient.

2.4. Clinical efficacy

The data presented by the MAH is for supporting this Grouped Type II /Type IB variation:

- The **Type II variation** is to extend the indication for Nexpovio to be used "*in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy*". In addition, the results from the pivotal study in support of this application were intended to fulfil the Specific Obligation (SOB) in the context of the Conditional Marketing Authorisation (CMA) of Nexpovio (selinexor) which was granted on 26 March 2021.
- The **Type IB variation** relates to the introduction of a new pack size (8 tablets per pack) for added convenience to patients for dose modification in the new intended treatment setting.

Table 1. Company-Sponsored Pivotal and Supportive Studies for Type II Variation

	Pivotal Study	Supportive Study
	KCP-330-023/BOSTON	**KCP-330-017/STOMP SVd Arm**
Protocol version	4	5
Number of patients	402	42
Indication	MM that has been previously treated with 1 to 3 anti-MM regimens	Relapsed/refractory MM
Study status	Ongoing	Ongoing[a]
Prior therapies	Patients who had at least 1 prior anti-MM regimen and no more than 3 prior anti-MM regimens. Induction therapy followed by stem cell transplant and consolidation/maintenance therapy was considered as 1 anti-MM regimen.	Patients whose MM was relapsing after ≥1 line of therapy
Dose	**SVd arm:** Selinexor: 100 mg PO on Days 1, 8, 15, 22, and 29 of each 35-day cycle Bortezomib: 1.3 mg/m^2 SC on Days 1, 8, 15, and 22 of each 35-day cycle Dexamethasone: 20 mg PO on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle **Vd arm:** **First 8 cycles:** Bortezomib: 1.3 mg/m^2 SC on Days 1, 4, 8, and 11 of each 21-day cycle. Dexamethasone: 20 mg PO dose on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle. **Cycles ≥9** Bortezomib 1.3 mg/m^2 SC on Days 1, 8, 15, and 22 of each 35-day cycle. Dexamethasone: 20 mg PO dose on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle. **SVdX arm:** Patients who crossed over from Vd treatment to SVdX following the Cycle 1 of SVd treatment as described above.	**Dose escalation:** **Selinexor QW schedule:** **1) Bortezomib QW schedule (35-day cycle), 7 patients** Selinexor: 80/100 mg PO QW on Days 1, 8, 15, 22, and 29 of each 35-day cycle Bortezomib: 1.3 mg/m^2 SC QW on Days 1, 8, 15, and 22 of each 35-day cycle Dexamethasone: 40 mg PO QW Days 1, 8, 15, 22, and 29 of each 35-day cycle **2) Bortezomib BIW schedule (21-day cycle), 6 patients** Selinexor: 80 mg PO QW on Days 1, 8, and 15 of each 21-day cycle Bortezomib: 1.3 mg/m^2 SC BIW on Days 1, 4, 8, and 11 of each 21-day cycle Dexamethasone: 40 mg PO QW Days 1, 8, and 15 of each 21-day cycle **Selinexor BIW schedule (35-day cycle), 9 patients:** Selinexor: 60/80 mg PO BIW on Days 1, 3, 8, 10, 15, 17, 22, and 24 of each 35-day cycle Bortezomib: 1.3 mg/m^2 SC QW on Days 1, 8, 15, and 22 of each 35-day cycle Dexamethasone: 20 mg PO BIW on Days 1, 3, 8, 10, 15, 17, 22, 24, 29, and 31 of each 35-day cycle
		Expansion, 20 patients: As of Protocol, v.3.0, the RP2D for SVd in the expansion phase was determined to be selinexor 100 mg + dexamethasone 40 mg + bortezomib 1.3 mg/m^2 SC, all QW. If a patient did not have at least a PR after 2 cycles at the RP2D (and had no AEs >Grade 2 [CTCAE 4.03] at the time of dose escalation), the Sd dose was escalated to selinexor 60 mg + dexamethasone 20 mg, BIW (total weekly selinexor dose = 120 mg).

Source: KCP-330-017 Protocol versions 3.0–5.0, KCP-330-017 CSR, KCP-330-023 Protocol version 4.0, KCP-330-023 CSR. AE: adverse event; BIW: twice weekly; CTCAE: Common Terminology Criteria for Adverse Events; MM: multiple myeloma; PO: orally; PR: partial response; QW: once weekly; RP2D: recommended Phase 2 dose; SC: subcutaneously; Sd: selinexor plus dexamethasone; SVd: selinexor plus bortezomib plus low-dose dexamethasone; SVdX: selinexor plus bortezomib plus low-dose dexamethasone treatment after crossover;
Vd: bortezomib plus low-dose dexamethasone.a Enrollment has been completed for SVd arm in KCP-330-017 (STOMP)

2.4.1. Dose response study

Phase 1b/2 Study KCP-330-017 (STOMP)

The STOMP study was a Phase 1b/2, multi-arm open label, multicenter, clinical study with **Dose Escalation** (Phase 1) and **Expansion** (Phase 2) to independently assess the maximum tolerated dose (**MTD**)/recommended Phase 2 dose (**RP2D**), safety, and efficacy of 7 treatment arms (selinexor in combination with backbone treatments) in patients with either newly diagnosed MM or previously treated MM.

Each arm started with a Dose Escalation Phase followed by a RP2D Expansion Phase.

Approximately 241 to 321 patients were considered needed for this study. This includes 96-186 patients in the Dose Escalation Phase and 145 patients in the Expansion Phase.

Phase 1 - Dose Escalation Phase (in SVd Arm):

Arm 2 (SVd) had **2 cohorts** to evaluate once-weekly (QW) vs. twice-weekly (BIW) selinexor dosing. The dose of selinexor was escalated from 80 mg to 100 mg in once-weekly cohorts and from 60 mg to 80 mg in twice-weekly cohorts, given with bortezomib once or BIW along with 'low dose' (40 mg weekly) dexamethasone.

Using the MTD results for both Cohorts, the SRC determine which MTD schedule will become the RP2D in the Expansion Phase.

Phase 2 – Expansion Phase

During the Expansion Phase, it was planned that a total of approximately 146-243 patients across the 7 Arms will receive the RP2D determined by the SRC for each Arm separately. Dose modifications to manage tolerability were allowed during the Expansion Phase.

Patients continued to receive treatment until disease progression (however patients may stay on treatment if they have clinical benefit per the Investigator), death, toxicity (i.e., adverse events (AEs) that cannot be managed with medical care), or withdrawal from the study. The study will end when all patients have completed the one-year Follow-up Period (i.e., when the last patient has died, been followed for 12 months after last dose of study drug (selinexor, bortezomib, or dexamethasone), been lost to follow-up, or has withdrawn consent, whichever occurs first).

The **RP2D established in the SVd arm** [Arm 2 SVd (selinexor +bortezomib + dexamethasone)] of STOMP was to be **used in the BOSTON study**.

Based on the results, the selected dose/regimen for further exploration in the BOSTON study was **selinexor 100 mg QW and bortezomib 1.3 mg/m2 QW plus dexamethasone 40 mg QW**.

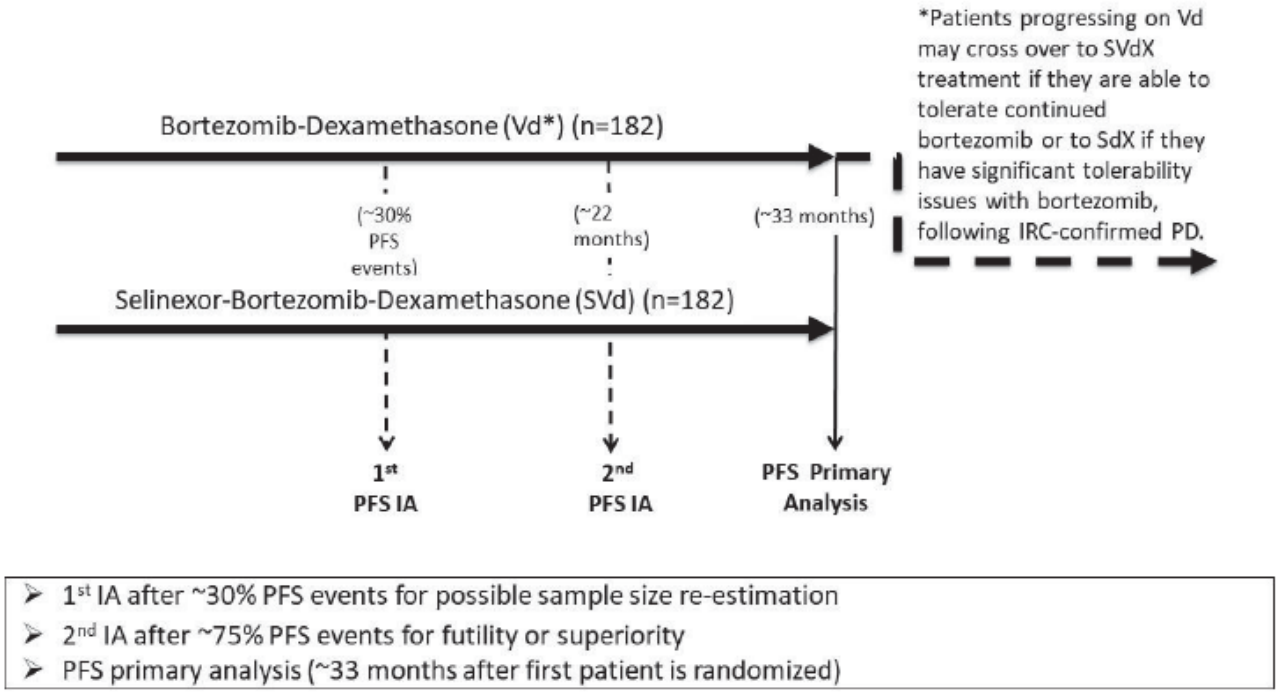
2.4.2. Main study: KCP-330-023/BOSTON study

KCP-330-023 is a confirmatory 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.

Methods

The study overview is presented in the Figure below:

Figure 1. BOSTON: Bortezomib, Selinexor, and Dexamethasone in Patients with Multiple Myeloma- Study Overview



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

Data cut-off:

- **Primary analysis**: Data cut-off date of 18 February 2020 (main efficacy data).
- **Updated analysis**: 15 February 2021.

Patients in the Vd Arm who have progressive disease (PD) that is confirmed by the Independent Review Committee (IRC) were 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 crossed over are 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 following process was used to prevent premature crossover:

- Investigators assessed PD according to the IMWG criteria, including repeat testing if PD was based on serum and/or urine M-protein, quantitative immunoglobulins for IgA/IgD, or serum free light chain (FLC). PD could also be based on new or enlarging plasmacytoma(s) or bone lesion(s) or on other symptoms and signs of clinical progression that met the IMWG criteria.
- All cases of PD were confirmed by the IRC prior to crossover.

- Crossover was not permitted based purely on Investigator assessed progression that did not meet any IMWG criteria for PD and could not be verified by IRC (e.g., deteriorating performance status).
- Crossover was not permitted if dosing of bortezomib was terminated before PD was confirmed by the IRC, unless termination of bortezomib was due to significant toxicities such as PN, and all treatment measures addressing these toxicities were exhausted and documented prior to bortezomib termination. Early termination of bortezomib was discussed and approved by the Sponsor's Medical Monitor in order to allow crossover to SdX after progression was confirmed by the IRC.
- Investigator assessed presumptive PD events that were not confirmed by the IRC had their PFS censored at the time of treatment discontinuation.

Multiple myeloma evaluations for both arms were done **every 3 weeks** from baseline on Cycle 1 Day 1 (C1D1) **through the first day of Week 37** (i.e. 12 MM evaluations occurred after C1D1) to identify patients who progressed quickly, **then every 5 weeks** for the remainder of the study, regardless of cycle length.

Dose modifications for selinexor to manage tolerability were allowed.

Independent Review Committee

An IRC was formed to review MM disease assessment data for this study, to independently assess disease response and time of PD.

PD based on site generated MM disease assessment data were to be confirmed by the IRC prior to discontinuing treatment from either arm (unless medically contraindicated).

PD as a result of plasmacytoma(s) or bone lesion(s) was to be reviewed by the IRC and results to be compared with baseline assessments.

IRC confirmation of PD was required for all patients and, for those patients in the Vd Arm, confirmation was required prior to initiation of SVdX treatment in the crossover. The IRC reviewed data (generated by the local and central laboratory) that was to be used for the final analysis of the primary endpoints.

The IRC's assessments of PFS and ORR were planned to be used as the basis for the evaluation of the primary endpoints.

Study participants

This study enrolled patients aged ≥18 years with RRMM who had received 1 to 3 prior anti-MM regimens and who met all of the inclusion criteria and none of the exclusion criteria.

Inclusion/exclusion criteria were assessed during Screening. Patients who met all of the inclusion criteria were enrolled in this study.

The main inclusion criteria were:

1. Histologically confirmed MM with measurable disease per IMWG guidelines as defined by at least one of the following:
    a) Serum M-protein ≥0.5 g/dL (>5 g/L) by serum protein electrophoresis (SPEP) or for IgA myeloma by quantitative serum IgA levels; or
    b) Urinary M-protein excretion at least 200 mg/24 hours; or
    c) Serum free light chain (FLC) ≥100 mg/L, provided that the serum FLC ratio is abnormal (normal FLC ratio: 0.26 to 1.65).
2. Have at least 1 prior anti-MM regimen and no more than 3 prior anti-MM regimens.

Figure 1. BOSTON: Bortezomib, Selinexor, and Dexamethasone in Patients with Multiple Myeloma- Study Overview

Induction therapy followed by stem cell transplant and consolidation/maintenance therapy were considered as 1 anti-MM regimen.

3. Documented evidence of progressive MM (based on the Investigator's determination according to the IMWG response criteria) on or after their most recent regimen.
4. Prior treatment with bortezomib or other PI was allowed, provided all of the following criteria were met:
    a) Best response achieved with prior bortezomib at any time was ≥PR and with the last PI therapy (alone or in combination) was ≥PR, AND
    b) Participant did not discontinue bortezomib due to Grade ≥3-related toxicity, AND
    c) Must have had at least a 6-month PI-treatment-free interval prior to C1D1 of study treatment.

Eligible patients were also required to have Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of ≤2 and adequate hepatic, renal and hematopoietic function.

Main exclusion criteria:

1. Prior exposure to a SINE compound, including selinexor.
2. Prior malignancy that required treatment or has shown evidence of recurrence (except for non-melanoma skin cancer or adequately treated cervical carcinoma in situ) during the 5 years prior to randomization. Cancer treated with curative intent for >5 years previously and without evidence of recurrence will be allowed.
3. Has any concurrent medical condition or disease (eg, uncontrolled active hypertension, uncontrolled active diabetes, active systemic infection, etc.) that is likely to interfere with study procedures.
4. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within 1 week prior to C1D1. Patients on prophylactic antibiotics or with a controlled infection within 1 week prior to C1D1 are acceptable.
5. Active plasma cell leukemia, documented systemic light chain amyloidosis; MM involving the central nervous system.
6. Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome.
7. Spinal cord compression.
8. Greater than Grade 2 peripheral neuropathy or Grade ≥2 peripheral neuropathy with pain at baseline, regardless of whether or not the patient is currently receiving medication.
9. Known intolerance, hypersensitivity, or contraindication to glucocorticoids.
10. Radiation, chemotherapy, or immunotherapy or any other anticancer therapy (including investigational therapies) ≤2 weeks prior to C1D1. Localized radiation to a single site at least 1 week before C1D1 is permitted. Glucocorticoids within 2 weeks of C1D1 are permitted. Patients on long-term glucocorticoids during Screening do not require a washout period but must be able to tolerate the specified dexamethasone dose in this study.
11. Prior autologous stem cell transplantation <1 month or allogeneic stem cell transplantation <4 months prior to C1D1.
12. Active graft versus host disease (after allogeneic stem cell transplantation) at C1D1.

13. Active, unstable cardiovascular function:

    a) Symptomatic ischemia, or

    b) Uncontrolled clinically significant conduction abnormalities (eg, patients with ventricular tachycardia on anti-arrhythmics are excluded; patients with first-degree atrioventricular block or asymptomatic left anterior fascicular block/right bundle branch block will not be excluded), or

    c) Congestive heart failure of New York Heart Association Class ≥3 or known left ventricular ejection fraction <40%, or

    d) Myocardial infarction within 3 months prior to C1D1.

14. Known active human immunodeficiency virus (HIV) infection or HIV sero-positivity. Known active hepatitis A, B, or C infection; or known to be positive for hepatitis C virus ribonucleic acid (RNA) or hepatitis B virus surface antigen.

Treatments

SVd arm:

- Selinexor: 100 mg PO on Days 1, 8, 15, 22, and 29 of each 35-day cycle
- Bortezomib: 1.3 mg/m2 SC on Days 1, 8, 15, and 22 of each 35-day cycle
- Dexamethasone: 20 mg PO on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle

Vd arm:

First 8 cycles:

- Bortezomib: 1.3 mg/m2 SC on Days 1, 4, 8, and 11 of each 21-day cycle.
- Dexamethasone: 20 mg PO dose on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle.

Cycles ≥9:

- Bortezomib 1.3 mg/m2 SC on Days 1, 8, 15, and 22 of each 35-day cycle.
- Dexamethasone: 20 mg PO dose on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle.

SVdX arm:

Patients who crossed over from Vd treatment to SVdX following the Cycle 1 of SVd treatment as described above.

Dose modifications for selinexor, dexamethasone, and bortezomib were allowed to manage tolerability.

Study **treatment** (SVd, Vd, or crossover) **continued until PD was confirmed by the IRC**, Investigator or patient decision to discontinue study treatment, pregnancy, unacceptable adverse events (AEs) or toxicity that could not be managed by supportive care, withdrawal of consent, death, or Sponsor decision to terminate the study.

PD confirmation by IRC was needed prior to discontinuation, unless medically contraindicated. An exception was allowed for patients in the Vd arm who terminated bortezomib treatment prior to IRC-confirmed PD if the termination was due to significant toxicities, such as PN, and all treatment measures addressing these toxicities were exhausted and documented prior to bortezomib termination. Early

termination of bortezomib was discussed and approved by the Sponsor's Medical Monitor in order to allow crossover to SdX after progression was confirmed by the IRC.

After IRC-confirmed PD:

- Patients in the SVd arm completed the End of Treatment Visit and were followed for survival.
- Patients in the Vd arm either crossed over or discontinued study treatment, completed the End of Treatment Visit, and were followed for survival

Crossover from the Vd arm to a treatment that included Sd ± bortezomib (i.e., SVdX or SdX) was allowed at the point of IRC-confirmed objective PD per the IMWG criteria for patients in the Vd arm.

Patients in the Vd arm who were able to tolerate continued bortezomib treatment were allowed to cross over to SVdX treatment.

Patients in the Vd arm who had significant tolerability issues with bortezomib (i.e., were unable to tolerate any continued bortezomib treatment (e.g., due to Grade >2 PN or Grade ≥2 PN with pain) were allowed to cross over to SdX treatment.

Selinexor Dose Escalation

A selinexor dose escalation may be considered up cycle 3 (C3) for patients being treated with a selinexor-containing regimen (ie, SVd Arm, SVdX treatment, or SdX treatment) who meet the following **3 criteria**:

1) do not achieve at least a PR within the first 2 cycles,
2) are tolerating SVd well at dose level 0, and
3) do not have any AEs related to study treatment Grade >2 (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.03) at the time of dose escalation. For Cycles ≥3, selinexor may be increased to a fixed oral 60 mg dose twice weekly during Weeks 1 through 5.

For patients who dose escalate, selinexor will be given as a fixed oral 60 mg dose on Days 1, 3, 8, 10, 15, 17, 22, 24, 29, and 31 of each 35-day cycle.

Dexamethasone (20 mg) will be given on the same days as selinexor.

Figure 2. SVd Arm Dose Schedule; 5-Week (35-Day) Cycle

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

Abbreviations: AE = adverse event; BIW = twice weekly; Bort = bortezomib; BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events; D = Day; Dex = dexamethasone; eCRF = electronic case report form; MM = multiple myeloma; NCI = National Cancer Institute; PR = partial response: QW = once weekly; SC = subcutaneous; Sel = selinexor; SVd = selinexor plus bortezomib plus low-dose dexamethasone. 1 Selinexor will be given as a fixed oral 100 mg dose QW. In no case may the selinexor dose exceed 70 mg/m2 per dose for any patient. If the patient's weight fluctuates substantially from baseline (i.e., > 20%) during SVd treatment, BSA should be recalculated. 2 Bortezomib will be given at a dose of 1.3 mg/m2 SC QW during Weeks 1 through 4, followed by a 13-day rest period. 3 Dexamethasone will be given as an oral 20 mg dose BIW (i.e., a total of 40 mg weekly). For patients who develop partial intolerance to glucocorticoids during the study (as determined by the Investigator), a dose reduction to a minimum dose of 10 to 12 mg dexamethasone BIW (i.e., a total of 20 to 24 mg weekly) is
permitted after a clear documentation of intolerance. Any dose reductions should be documented in the patient's research record and the eCRF. 4 Selinexor will be given as a fixed oral 60 mg dose BIW during Weeks 1 through 5 of Cycles ≥ 3. If the patient's weight fluctuates substantially from baseline (i.e., > 20%) during SVd treatment, BSA should be recalculated.

Duration of Treatment and Follow-up

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

After discontinuation of SVd, Vd, SVdX, or SdX patients will be followed for survival every 3 months until the end of study (ie, when the last patient treated in the study has been followed for up to 5 years after their last dose of SVd/Vd/SVdX/SdX treatment).

Objectives

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

Primary Objective

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

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

Exploratory Objectives

- To evaluate PFS and ORR in patient subsets based on the IMWG Revised International Staging System (R-ISS) criteria and International Staging System (ISS) criteria (Palumbo et al., 2015), in patients randomized to the SVd Arm versus the Vd Arm
- To compare time to discontinuation of SVd and Vd treatment in patients randomized to the SVd Arm versus the Vd Arm

  To compare health-related quality of life (HR-QoL) outcomes as measured by the EORTC core quality of life (QLQ-C30) instrument and the EuroQoL Group Health (EQ-5D-5L) instrument in patients randomized to the SVd Arm versus the Vd Arm
- To correlate incidence and severity of peripheral neuropathy by AE reports with QLQCIPN20 outcomes
- To assess disease response to SdX treatment

Outcomes/endpoints

Primary efficacy endpoint for the BOSTON study:

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

Key secondary efficacy endpoints were:

- **ORR**, defined as any response ≥ partial response (PR) (i.e., PR, very good partial response [VGPR], complete response [CR], or stringent complete response [sCR]) based on the IRC's response outcome assessments, according to the IMWG response criteria.
- 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 minimal residual disease-negative (for patients who achieved a CR or sCR).

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.

Secondary HR-QoL Endpoint

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

Figure 2. SVd Arm Dose Schedule; 5-Week (35-Day) Cycle

Exploratory Endpoints

- Time to discontinuation of SVd and Vd treatment
- HR-QoL, as measured by the EORTC QLQ-C30 and the EQ-5D-5L instruments
- Disease response to SdX treatment according to the IMWG response criteria

Sample size

The **sample size** was designed to have **80% power** to detect a **median time to PFS** for patients treated with **SVd** of **13.5 months** versus patients treated with **Vd** of **9.4 months**, using a **1-sided alpha of 0.025**, 15 months accrual and 18 months follow up, and a 1:1 allocation of treatment to SVd:Vd, and allowing for an interim analysis (IA) of PFS (second IA) for futility or superiority, with the treatment difference assessed by a log-rank test.

Based on these statistical assumptions, **a total of 267 PFS events were required for the final analysis**. To achieve these events, a total of approximately **364 patients** (~**182 patients/arm**) were required for enrolment.

The justification of a median time to PFS of **9.4 months** in the Vd Arm was based on previous clinical studies (ENDEAVOR and CASTOR), both of which had similar eligibility criteria to the BOSTON study where PFS was **9.4 months** (Dimopoulos et al., 2016) and **7.2 months**, respectively (Palumbo et al., 2016). Median time to PFS in the SVd Arm was based on preliminary results from Karyopharm's STOMP study (Study KCP-330-017). An exponential dropout rate of 0.65% per month (equivalently approximately 10% dropout after 18 months) is assumed.

Randomisation

Patients were randomized in a **1:1 ratio to 1 of the 2 treatment arms** (**SVd** or **Vd**). Randomization was stratified for prior PI therapy (yes or no), number of prior anti-MM regimens (1 versus >1 and disease severity at study entry (based on the revised International Staging System [**R-ISS**]; **Stage III** versus **Stage I or II**).

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

- **SVd arm**: selinexor (QW) + SC bortezomib (QW) + dexamethasone.
- **Vd arm**: SC bortezomib (Cycles 1-8 BIW, Cycles ≥9 QW) + 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)

— Revised International Staging System (**R-ISS**) stage at study entry based on screening results (R-ISS Stage III versus R-ISS Stage I or II) (Palumbo 2016). If data for chromosomal abnormalities and serum lactate dehydrogenase required for R-ISS staging were not available, patients were assigned to the R-ISS category corresponding to their International Staging System (ISS) stage.

Figure 2. SVd Arm Dose Schedule; 5-Week (35-Day) Cycle

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

Blinding (masking)

Not applicable, as this was a 2-arm, open-label study.

Statistical methods

Changes to the Planned Analyses

There were 3 versions of the SAP (Version 1.0 dated 15 August 2018, Version 2.0 dated 30 September 2019, and Version 3.0 dated 24 February 2020).

Summary of Major Changes to Statistical Analysis Plan:

Version	***Summary of Major Changes***
Version 3.0 (24 February 2020)	Provided the results of the first IA. • Changed timing of the final PFS analysis to when the second IA was originally planned (i.e., after 201 PFS events occurred). • Removed the CHW method since sample size did not change after the first IA. • Removed the type I error adjustment for the second IA since the second IA will be treated as final analysis. • Added more details to the definition of TEAE. • Modified the Adverse Event of Clinical Interest (AECI) categories.
Version 2.0 (30 September 2019)	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 the SVdX treatment only) or dexamethasone for the SVdX (SdX) treatment after crossover • 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 adverse events or concomitant medications — Definition of concomitant medications — The end date of the Vd treatment — TEAE definition after crossover to the SVdX/SdX treatment • Clarified the PP population definition • Clarified that the best response and duration of the most recent prior anti-MM regimen will be summarized • Modified the calculation of the duration of the most recent prior anti-MM regimen in days • Removed region as the stratum used for analyses and clarified that the stratification factors include prior PI therapies, the number of prior anti-MM regimens, and R-ISS stage at study entry • Clarified the censoring criteria for patients who do not have an event in the corresponding sections • Modified "Adverse Event of Special Interest (AESI)" to "AECI" • Modified the AECI categories

Source: SAP Version 3.0 Section 1.8. MM=multiple myeloma; PI=proteasome inhibitor; SdX=selinexor plus low-dose dexamethasone treatment after crossover; SVdX=selinexor plus bortezomib plus low-dose dexamethasone treatment after crossover; Vd=bortezomib plus low-dose dexamethasone

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.

Figure 2. SVd Arm Dose Schedule; 5-Week (35-Day) Cycle

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. 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.

Study hypothesis: Superiority

Interim analyses

Two interim analyses for primary PFS endpoint are planned.

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).

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 was 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 MAH proposed to use the second IA as the final efficacy analyses no matter the outcome is positive or not. With DSMB agreement, the second IA was used as the final PFS analysis and used all one-sided alpha of 0.025.

The null hypothesis of PFS endpoint will not be re-tested at any subsequent timepoint.

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.

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

Primary endpoint

PFS: 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.

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, d. documented treatment discontinuation e. start of new MM treatment, whichever occurs first	Date of last adequate disease assessment on or prior to the earliest occurrence of the events (a. – e.) listed in the left column	Censored

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

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.

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 rates for ≥ VGPR based on the IRC's assessment

Regarding secondary endpoints, specifically for OS analysis, 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).

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).

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.

Graphical illustration of the propagation of endpoint-specific alpha

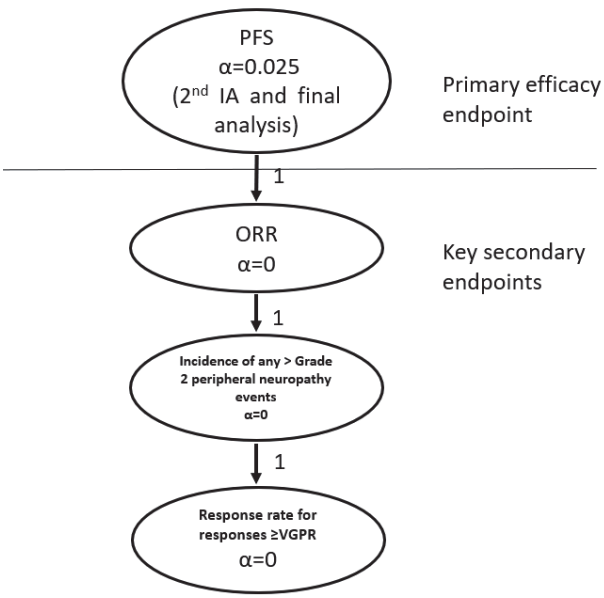


Figure 2. SVd Arm Dose Schedule; 5-Week (35-Day) Cycle

The updated analysis based on the data cut-off date of 15 Feb 2021 was conducted per CHMP request. The updated analysis is non-inferential and the p-values from the updated analysis were nominal.

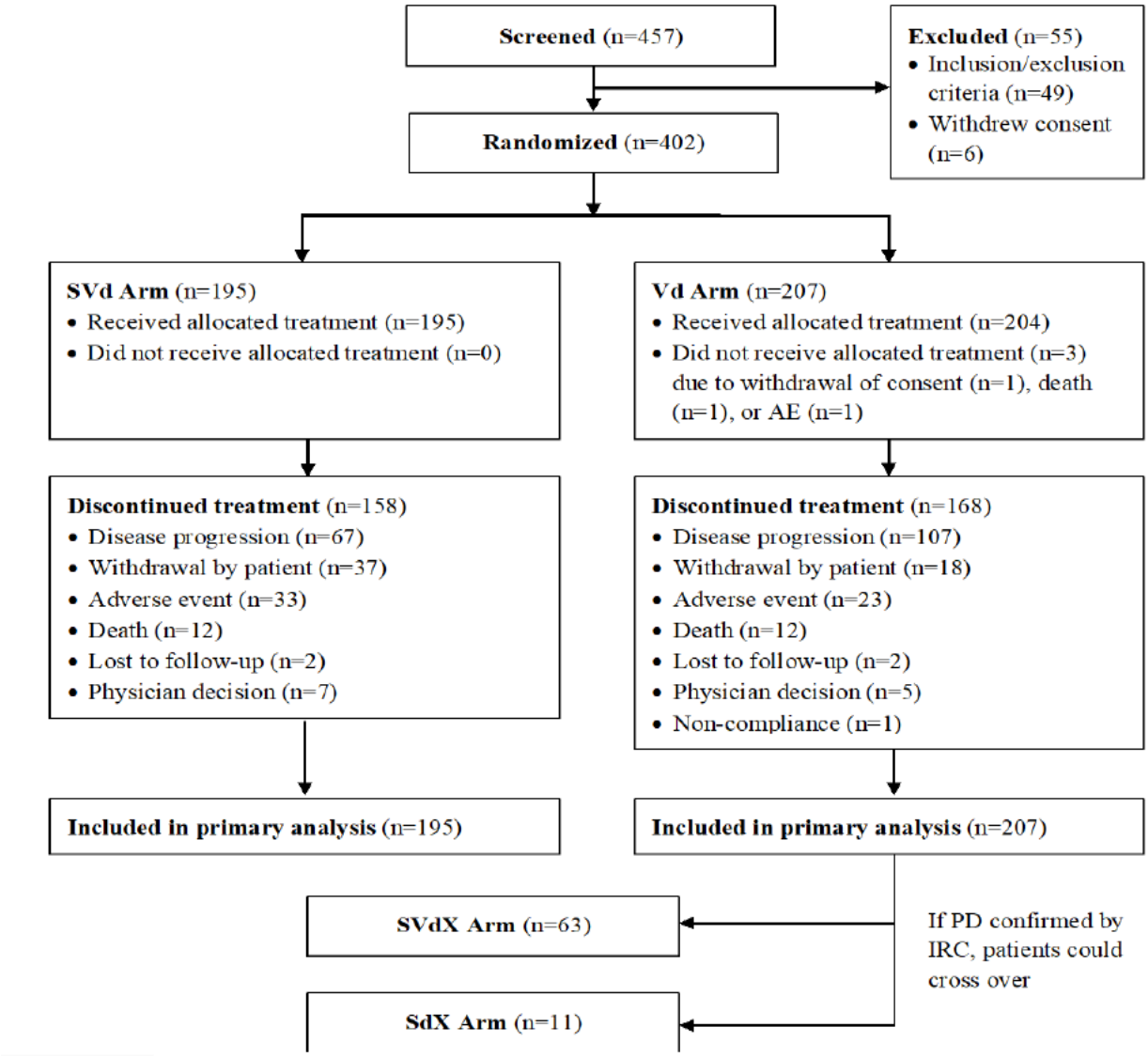
Results

Participant flow

A total of 457 patients were screened for inclusion in the study; 402 patients were randomized, and 399 patients received at least one dose of study treatment.

Of the 402 randomized patients, 195 were randomized onto the SVd arm (all dosed) and 207 patients were randomized to the Vd arm, of which 204 were dosed. Three patients randomized to the Vd arm were not dosed due to withdrawal of consent, death, and AE.

Figure 3. CONSORT Diagram of Patient Disposition in Study KCP-330-023. Primary Analysis



Source: Table 14.1.1.1, Table 14.1.1.2. Data cut-off date: 18 Feb 2020.
AE=adverse event; IRC=independent review committee; PD=progressive disease; SdX=selinexor plus low-dose dexamethasone treatment after crossover; SVd=selinexor plus bortezomib plus low-dose dexamethasone; SVdX=selinexor plus bortezomib plus low-dose dexamethasone treatment after crossover; Vd=bortezomib plus low dose dexamethasone.

At the time of the udpdated cut-off (DBL: 15 Feb 2021) the distribution in terms of treatment discontinuations and patients on treatment was as included in the table below.

Table 2. Patients Disposition- Updated analysis

Disposition Category	SVd Arm (N=195 n (%)	Vd Arm (N=204) n (%)	Total (N=399) n (%)
Total Number of Patients Screened			457
Total Number of Randomized Patients	195	207	402
End of Treatment			
On-treatment	21 (10.8)	16 (7.8)	37 (9.3)
Discontinued Treatment and Reasons	174 (89.2)	188 (92.2)	362 (90.7)
Disease Progression	76 (39.0)	118 (57.8)	194 (48.6)
Withdrawal by Patient	37 (19.0)	21 (10.3)	58 (14.5)
Adverse Event[b]	33 (16.9)	26 (12.7)	59 (14.8)
Death	14 (7.2)	14 (6.9)	28 (7.0)
Lost to Follow-up	3 (1.5)	2 (1.0)	5 (1.3)
Non-compliance with Study Drug/Protocol Deviation	1 (0.5)	2 (1.0)	3 (0.8)
Physician Decision	10 (5.1)	5 (2.5)	15 (3.8)
End of Study			
On-study	73 (37.4)	78 (38.2)	151 (37.8)
Discontinued from Study and Reasons	122 (62.6)	126 (61.8)	248 (62.2)
Withdrawal by Patient	39 (20.0)	39 (19.1)	78 (19.5)
Death	68 (34.9)	79 (38.7)	147 (36.8)
Lost to Follow-up	12 (6.2)	7 (3.4)	19 (4.8)
Physician Decision	1 (0.5)	0	1 (0.3)
Other	2 (1.0)	1 (0.5)	3 (0.8)

Source: Table 14.1.1.1_updated. Data cut-off date: 15 Feb 2021.
SVd=selinexor plus bortezomib plus low-dose dexamethasone; Vd=bortezomib plus low-dose dexamethasone.
a Three patients were randomized but did not receive any dose of study drug due to withdrawal of consent, death or AE. b Includes toxicity to study drug.

Table 3. Patients on Treatment or in Follow-up

Patients on Treatment or in Follow-up – Primary Analysis

Disposition Category	SVd Arm (N=195) n (%)	Vd Arm (N=204) n (%)	Total (N=399) n (%)
Patients On Treatment	37 (19.0)	36 (17.6)	73 (18.3)
Patients in Survival Follow-up[a]	65 (33.3)	51 (25.0)	116 (29.1)
Patients Who Discontinued From the Study Without Completing 5-year Survival Follow-up			

Source: Table 14.1.1.1. Data cut-off date: 18 Feb 2020. SVd=selinexor plus bortezomib plus low-dose dexamethasone; Vd=bortezomib plus low-dose dexamethasone. a Patients in follow-up consists of patients who are willing to continue into Survival Follow-up, still alive, not lost to follow-up and have not discontinued from the study.

– Updated Analysis

SVd Arm (N=195) n (%)	Vd Arm (N=204) n (%)	Total (N=399) n (%)
21 (10.8)	16 (7.8)	37 (9.3)
52 (26.7)	58 (28.4)	110 (27.6)
13 (6.7)	16 (7.8)	29 (7.3)

Source: Table 14.1.1.1_updated. Data cut-off date: 15 Feb 2021. SVd=selinexor plus bortezomib plus low-dose dexamethasone; Vd=bortezomib plus low-dose dexamethasone. a Patients in follow-up consists of patients who are willing to continue into Survival Follow-up, still alive, not lost to follow-up and have not discontinued from the study.

As of the data cut-off date of **18 Feb 2020 (primary analysis)**, the median follow-up was 17.3 months in the SVd arm and 17.5 months in the Vd arm. In the **updated analysis (15 Feb 2021)**, the median follow-up was 28.71 months in the SVd arm and 28.65 months in the Vd arm.

The most common reasons for overall treatment discontinuation were PD (174 patients [43.6%]), withdrawal by patient (55 patients [13.8%]), and AEs (56 patients [14.0%]). More patients discontinued due to PD in the Vd arm compared to the SVd arm (52.5% versus 34.4%).

Discontinuations due to deaths on or within 30 days of last dose of treatment were similar in the 2 arms. However, there were more discontinuations due to AEs in the SVd arm versus the Vd arm (16.9% versus 11.3%).

Recruitment

- First patient treated: 07 June 2017
- Last patient completed: 21 October 2016
- Date of Data Cut-Off (Primary analysis): 18 February 2020
- Date of Data Cut-Off (Updated analysis): 15 February 2021

Study Locations

This multicenter study was conducted at 165 clinical investigative sites in 21 countries. Of the 165 investigative sites, 123 sites enrolled 402 patients in the study.

Conduct of the study

Summary of Major Changes Made in Protocol Amendments

Amendment	***Summary of Major Changes***
Amendment 3, Version 4.0 (17 August 2018)	• Changed ORR from a primary endpoint to a key secondary endpoint to address concerns expressed by the Agencies regarding including ORR as a primary endpoint (i.e., an analysis of ORR could jeopardize the integrity of the study for the ultimate assessment of PFS) • Revised the definition of "IRC-confirmed PD" and renamed the term as "IRC PD confirmation." • Added a description of 8 tumor lysis syndrome cases reported across all of selinexor development as of May 2018/ • Removed the split of the alpha level between PFS (0.02) and ORR (0.005) and added the assumed exponential dropout rate of 0.65% • Revised the total number of PFS events required for the final analysis from 284 to 267, for the IA for sample size re-estimation from 85 to 81, and for the IA for futility or superiority from 213 to 201 • Removed the secondary OS1 objective/endpoint • Removed the secondary objective/endpoint comparing ORR, PFS, and DOR for patients with 1 versus >1 prior anti-MM regimen and added it as a subgroup exploratory analysis • Revised the basis for the determination of the Revised International Staging System stage used in stratification of randomization from "at original MM diagnosis" to "at study entry, based on screening results." • Added an exception to the requirement that patients were to either remain on the study treatment until PD was confirmed by the IRC or until the patient discontinued the study treatment, completed the End of Treatment Visit, and was followed for survival. The exception only applied to patients in the Vd arm who had to terminate bortezomib prior to IRC-confirmed PD due to significant toxicities • Revised inclusion criterion #12 for contraception requirements and guidance for pregnancy and breastfeeding

	• Clarified the wording for how selinexor should be administered and removed the need to take selinexor with food • Revised the guidance for the doses of the study treatment that had to be missed due to protocol- or study-related reasons to: 1) Provided 72 hours between 2 consecutive doses of bortezomib and 2) Removed the requirement for 36 hours between doses • Updated the supportive care instructions for consistency with the current clinical practice • Deleted the restriction for alcohol use on the study treatment dosing days • Added text in a new subsection to indicate that a portion of the bone marrow aspirate was to be collected to isolate plasma, non-tumor CD138-, and tumor CD138+ cell fractions for subsequent pharmacodynamic studies • Removed the North American restriction for pharmacokinetic sampling
	• Added the specific grading system (i.e., the American Optometric Association) for cataract/lens opacity • Added a new subsection with text clarifying the definition of events that did not meet the definition of a serious AE • Changed the reporting mechanism for reporting overdose, abuse, misuse, medication errors, and occupational exposure from fax to email • Revised the timing for reporting of overdose, abuse, misuse, medication errors, and occupational exposure for events that were not AEs or serious AEs from "as soon as possible" to "within 24 hours of awareness." • Moved OS from a key secondary efficacy endpoint to a non-key secondary efficacy endpoint • Moved response rates for responses ≥ very good partial response from #2 to #3 (to replace OS) • Removed the following from the analysis of the secondary endpoint of ORR1: "It is expected that approximately 70 patients will cross over from the Vd arm to SVdX. This sample size results in a power of 92% assuming an ORR1 of 25% and 1-sided type I error of 0.025." • Added details for the cytogenetic alteration analyses • A definition of clinical progression was added for the primary analysis of PFS • Added the following sensitivity analysis: Comparison of PFS endpoint by treatment based on Investigator's assessment • Aligned the points, analyses, and concomitant medications with the Statistical Analysis Plan • Aligned the safety sections with the new safety language template provided by the Karyopharm Pharmacovigilance Department
Amendment 2, Version 3.0 (06 April 2017)	• Added details for the Interactive Response Technology system that was to used to perform treatment randomization • Added details for continuation of the study treatment for patients if the study was terminated early to comply with International Council for Harmonization Good Clinical Practice E6 • Clarified that double-barrier contraception methods were considered effective but not highly effective to align with the recommendations of the Clinical Trial Facilitation Group. Also clarified that sexual partners who were surgically sterilized were not exempt from the contraception requirements unless they were "permanently" surgically sterilized • Added the requirement for pregnancy testing (serum human chorionic gonadotropin or urine) for females of childbearing potential before dosing on Day 1 of Cycles ≥2 to align with the recommendations of the Clinical Trial Facilitation Group • For the PFS primary efficacy endpoint, changed the analysis to the stratified log-rank test and stratified Cox model (previously in Version 1.0 of the protocol). Also, specified that the stratified log-rank test was to be used for the secondary analyses of OS, DOR, and OS1, and that the exploratory analysis of the treatment discontinuation rate was to be performed using the stratified log-rank test • For the ORR efficacy analysis, specified that patients missing MM disease assessments after C1D1 were to be imputed as non-responders • Changed the timing of the secondary analyses from "after significance is reached for PFS" to "at the time of ORR analysis" and specified that "statistical significance of the secondary endpoints will not be claimed until the ORR and PFS have reached significance."

	• Changed the Hochberg procedure for testing the secondary endpoints to a hierarchical testing procedure
Amendment 1, Version 2.0 (22 February 2017)	• Added crossover to treatment with selinexor and dexamethasone (SdX) as an option for patients in the Vd arm after PD was confirmed by the IRC if they had significant tolerability issues with bortezomib (e.g., higher than Grade 2 PN or Grade 2 or higher PN with pain) • Changed the third key secondary efficacy objective/endpoint from DOR to OS • Revised the OS1 and time-to-next-treatment secondary objectives to add SdX and added a new exploratory objective (i.e., to assess disease response to SdX treatment) and endpoint (i.e., IMWG response criteria for patients treated with SdX) for SdX to assess response for patients who crossed over to SdX. Also clarified that for OS1, patients on the Vd arm who crossed over were censored at the date of crossover • Revised the definition of the time to response to "the duration of the time from randomization to the first documented response (≥PR) per IMWG response criteria" • Updated the IMWG response criteria for myeloma to align with the most recent IMWG criteria (Kumar 2016). The definition for minimal residual disease was changed from "minor" to "minimal" response to align with the IMWG Consensus Criteria • The process for crossover was modified to prevent premature crossover • Revised exclusion #12 to clarify that patients treated with an investigational anticancer therapy within 2 weeks before C1D1 were specifically excluded from the study • Clarified that symptom-directed physical examinations were only to be performed if clinically indicated • Clarified that clinical plasmacytoma assessments are to be performed if clinically indicated at MM Disease Assessment Visits and at Durability of Response and Survival Follow-up Visits. Also corrected the window for detection of plasmacytomas at baseline by physical examination/palpation from "within 45 days" to "within 28 days" before C1D1 • Clarified that a skeletal survey was required at the End of Treatment Visit
	• Removed the requirement for dose escalation for patients in the SVd arm who did not achieve at least a PR within the first 2 cycles, are tolerating SVd well, and did not have any AEs related to the study treatment that were higher than Grade 2 at the time of the dose escalation • Added a requirement for baseline bone marrow aspirate at Screening for all patients. Also, clarified that a portion of the bone marrow aspirate collected at Screening was to be provided to the central laboratory for karyotyping and fluorescence in situ hybridization analysis to confirm diagnosis and classify cytogenetic MM subtypes for Revised International Staging System staging • Removed turbidometry as an acceptable method for measuring quantitative Ig levels. Also clarified that nephelometry could be used in place of serum protein electrophoresis for routine M-protein measurement for patients with IgD myeloma in addition to patients with IgA myeloma • Added pharmacokinetic assessments for bortezomib and selinexor in a subset of patients randomized to each arm (i.e., the Vd arm and the SVd arm) • Clarified that body surface area was to be recalculated if the patient's weight fluctuates substantially from baseline (i.e., >20%) during treatment (including Vd, SVd, SVdX, and SdX) • Revised the definition of the per-protocol population from all intent-to-treat patients who had received "any amount" to "at least 1 dose "of the study treatment • Added a justification for the sample size calculation assumptions • Specified that an independent third party (the Data Safety Monitoring Board) was to conduct and review the sample size re-estimation and that an interim analysis charter was to be created to outline the operational procedures associated with both PFS IAs • Clarified the timing and details for the second IA • Added a sensitivity analysis using the Breslow-Day test to evaluate the homogeneity of the odds ratios across the strata associated with the ORR endpoint and the 2 secondary efficacy endpoint analyses which were analyzed using the Cochran-Mantel-Haenszel test • Added a sensitivity analyses for the primary efficacy endpoint and key secondary efficacy endpoints • Clarified that all changes in MM disease assessments were based on baseline MM disease assessments from C1D1 of the study treatment • Added a method for testing the proportional hazard assumption associated with the analyses of the primary and key secondary time-to-event endpoints

	• Provided additional details, including subgroups, for the exploratory analyses • Revised the correction for QT corrected interval from Bazett's to Fridericia's • Text for safety definitions, recording, and reporting revised

Baseline data

Patients were enrolled at 165 sites in 21 countries, grouped into 4 regions

Table 4. Enrolment by Region and Country (Intent-to-Treat Population)

Region/ Country n (%)	SVd Arm (N=195)	Vd Arm (N=207)	Total (N=402)
Region 1	**18 (9.2)**	**18 (8.7)**	**36 (9.0)**
Canada	5 (2.6)	11 (5.3)	16 (4.0)
United States of America	13 (6.7)	7 (3.4)	20 (5.0)
Region 2	**61 (31.3)**	**66 (31.9)**	**127 (31.6)**
Australia	12 (6.2)	9 (4.3)	21 (5.2)
Austria	4 (2.1)	5 (2.4)	9 (2.2)
Belgium	0	3 (1.4)	3 (0.7)
France	6 (3.1)	10 (4.8)	16 (4.0)
Germany	3 (1.5)	5 (2.4)	8 (2.0)
Israel	3 (1.5)	2 (1.0)	5 (1.2)
Italy	6 (3.1)	12 (5.8)	18 (4.5)
Spain	8 (4.1)	3 (1.4)	11 (2.7)
United Kingdom of Great Britain	19 (9.7)	17 (8.2)	36 (9.0)
Region 3	**47 (24.1)**	**53 (25.6)**	**100 (24.9)**
Czech Republic	15 (7.7)	18 (8.7)	33 (8.2)
Greece	14 (7.2)	15 (7.2)	29 (7.2)
Hungary	3 (1.5)	0	3 (0.7)
Poland	15 (7.7)	20 (9.7)	35 (8.7)
Region 4	**69 (35.4)**	**70 (33.8)**	**139 (34.6)**
Bulgaria	6 (3.1)	6 (2.9)	12 (3.0)
India	23 (11.8)	20 (9.7)	43 (10.7)
Romania	0	6 (2.9)	6 (1.5)
Russian Federation	12 (6.2)	7 (3.4)	19 (4.7)
Serbia	4 (2.1)	10 (4.8)	14 (3.5)
Ukraine	24 (12.3)	21 (10.1)	45 (11.2)

Source: Table 14.1.2.1. SVd=selinexor plus bortezomib plus low-dose dexamethasone; Vd=bortezomib plus low-dose dexamethasone.

The median ages of the patients in BOSTON were 66 and 67 years in the SVd and Vd arms, respectively. The majority of the patients were 65 years of age or older (SVd, 55.9%; Vd, 63.8%) and ~20% were ≥75 years of age. More males were enrolled in the study than females (males: SVd, 59.0%; Vd, 55.6%) and the race was predominantly White (SVd, 82.6%; Vd, 79.7%).

Table 5. Patient Demographics (Intent-to-Treat Population)

	SVd Arm (N=195)	Vd Arm (N=207)	Total (N=402)
Age (Years)[a]			
N	195	207	402
Median	66.0	67.0	67.0
Min, Max	40, 87	38, 90	38, 90
Age Category n (%)[a]			
18 – 50	15 (7.7)	11 (5.3)	26 (6.5)
51 – 64	71 (36.4)	64 (30.9)	135 (33.6)
65 – 74	75 (38.5)	85 (41.1)	160 (39.8)
≥ 75	34 (17.4)	47 (22.7)	81 (20.1)
Sex n (%)			
Male	115 (59.0)	115 (55.6)	230 (57.2)
Female	80 (41.0)	92 (44.4)	172 (42.8)
Race n (%)			
Asian	25 (12.8)	25 (12.1)	50 (12.4)
Black or African American	4 (2.1)	7 (3.4)	11 (2.7)
White	161 (82.6)	165 (79.7)	326 (81.1)
Other	0	1 (0.5)	1 (0.2)
Missing	5 (2.6)	9 (4.3)	14 (3.5)
Ethnicity n (%)			
Hispanic or Latino	6 (3.1)	5 (2.4)	11 (2.7)
Not Hispanic or Latino	171 (87.7)	188 (90.8)	359 (89.3)
Not Reported	14 (7.2)	11 (5.3)	25 (6.2)
Unknown	4 (2.1)	2 (1.0)	6 (1.5)
Missing	0	1 (0.5)	1 (0.2)

Source: Table 14.1.2.1. Max=maximum; min=minimum; SVd=selinexor plus bortezomib plus low-dose dexamethasone; Vd=bortezomib plus low-dose dexamethasone. a Age is the age at date of randomization.

Baseline disease characteristics were well balanced across the 2 arms:

- ECOG PS: score of 0-1; SVd, 89.8%; Vd, 92.3%
- Median time from diagnosis: SVd, 3.8 years; Vd, 3.6 years
- R-ISS stage: score I or II: SVd, 88.7%; Vd, 85.5%
- Renal function: CrCl of 30-<60 or ≥60 mL/min: SVd, 27.2% and 71.3%; Vd, 29.0%and 66.2%
- High-risk chromosomal abnormalities (including: del[17p]/p53, t[14;16], t[4;14],1q21): SVd, 49.7%; Vd, 45.9%

Table 6. Baseline Disease Characteristics (Intent-to-Treat Population)

	SVd Arm (N=195)	Vd Arm (N=207)	Total (N=402)
Baseline ECOG Performance Status n (%)			
0	69 (35.4)	77 (37.2)	146 (36.3)
1	106 (54.4)	114 (55.1)	220 (54.7)
2	20 (10.3)	16 (7.7)	36 (9.0)
Time from Initial Diagnosis (Years)[a]			
N	195	207	402
Median	3.81	3.59	3.70
Min, Max	0.4, 23.0	0.4, 22.0	0.4, 23.0
Creatinine Clearance at Baseline (mL/min), n (%)			
<30	3 (1.5)	10 (4.8)	13 (3.2)
30 - <60	53 (27.2)	60 (29.0)	113 (28.1)
≥60	139 (71.3)	137 (66.2)	276 (68.7)
R-ISS Stage at Screening, n (%)			
I	56 (28.7)	52 (25.1)	108 (26.9)
II	117 (60.0)	125 (60.4)	242 (60.2)
III	12 (6.2)	16 (7.7)	28 (7.0)

	SVd Arm (N=195)	Vd Arm (N=207)	Total (N=402)
Not available	10 (5.1)	14 (6.8)	24 (6.0)
% Plasma Cells at Initial Diagnosis			
N	169	170	339
Median	33.7	40.0	35.6
Min, Max	0.0, 99.0	0.0, 95.0	0.0, 99.0
% Plasma Cells at Initial Diagnosis, n (%)			
<50	116 (59.5)	100 (48.3)	216 (53.7)
≥50	53 (27.2)	70 (33.8)	123 (30.6)
Patients with High-Risk Chromosomal Abnormalities (Baseline or Initial Diagnosis), n (%)[b]			
del (17p)/p53	21 (10.8)	16 (7.7)	37 (9.2)
t (14;16)	7 (3.6)	11 (5.3)	18 (4.5)
t (4;14)	22 (11.3)	28 (13.5)	50 (12.4)
1q21	80 (41.0)	71 (34.3)	151 (37.6)
Any of del(17p)/p53, t(14;16), t(4;14), 1q21	97 (49.7)	95 (45.9)	192 (47.8)
Patients with Other Gene Mutations (Baseline or Initial Diagnosis):[b]			
del(13)	16 (8.2)	17 (8.2)	33 (8.2)
t(6;14)	0	0	0
t(11;14)	17 (8.7)	12 (5.8)	29 (7.2)
t(14;20)	2 (1.0)	1 (0.5)	3 (0.7)

Source: Table 14.1.3.1, Table 14.1.4.1.1, Table 14.1.4.1.2, Table 14.1.4.1.4.
ECOG=Eastern Cooperative Oncology Group; max=maximum; min=minimum; R-ISS=The Revised International Staging System; SVd=selinexor plus bortezomib plus low-dose dexamethasone; Vd=bortezomib plus low-dose dexamethasone. a Time from initial diagnosis to date of randomization (prior to dosing at Cycle 1 Day 1). b These are not mutually exclusive genetic abnormalities (patients may have >1 abnormality). Of note, 56 (28.7%) patients in the SVd arm and 70 (33.8%) in the Vd arm had moderate to severe renal dysfunction with a creatinine clearance of <60 mL/min at baseline.

As expected, patients in the BOSTON study had multiple ongoing comorbidities at baseline, (median of 4 for both arms; Module 2.7.3, Section 3.1.4). Of note the most frequent comorbidity was cataract as seen in 60% and 62.3% of patients in the SVd and Vd arm respectively. Additional frequent comorbidities

included hypertension (SVd, 45.6%; Vd, 49.3%), PN (SVd, 12.3%; Vd, 15.5%), hypothyroidism (SVd, 11.3%; Vd, 5.3%), and type 2 diabetes mellitus (SVd, 10.3%; Vd, 7.7%).

Approximately 50% of the patients had received 1 **prior anti-MM therapy** (SVd, 50.8%; Vd, 47.8%) with one-third having 2 prior regimens, and the remainder having 3 prior regimens for MM.

Table 7. Prior Anti-myeloma Therapies (Intent-to-Treat Population)

	SVd Arm (N=195)	Vd Arm (N=207)	Total (N=402)
Patients Who Received any Prior Anti-MM Drugs, n (%)	195 (100.0)	207 (100.0)	402 (100.0)
Number of Unique Prior Anti-MM Drugs			
Median	5.0	5.0	5.0
Min, Max	1, 9	1, 9	1, 9
Number of Prior Anti-MM Regimens, n (%)			
1	99 (50.8)	99 (47.8)	198 (49.3)
2	65 (33.3)	64 (30.9)	129 (32.1)
3	31 (15.9)	44 (21.3)	75 (18.7)
Number of Prior Anti-MM Regimens			
Mean (STD)	1.7 (0.74)	1.7 (0.79)	1.7 (0.77)
Min, Max	1, 3	1, 3	1, 3
Prior PI Therapies, n (%)			
Yes	148 (75.9)	159 (76.8)	307 (76.4)
No	47 (24.1)	48 (23.2)	95 (23.6)
Prior Anti-myeloma Drugs, n (%)			
Bortezomib	134 (68.7)	145 (70.0)	279 (69.4)
Carfilzomib	20 (10.3)	21 (10.1)	41 (10.2)
Ixazomib	6 (3.1)	3 (1.4)	9 (2.2)
Daratumumab	11 (5.6)	6 (2.9)	17 (4.2)
Lenalidomide	77 (39.5)	77 (37.2)	154 (38.3)
Pomalidomide	11 (5.6)	7 (3.4)	18 (4.5)
Prior Stem Cell Transplant n (%)	76 (39.0)	63 (30.4)	139 (34.6)
Patients Who Received any Prior Anti-MM Radiotherapy, n (%)	30 (15.4)	41 (19.8)	71 (17.7)

Source: Table 14.1.5.1.1, Table 14.1.5.1.2. Max= maximum; min=minimum; MM=multiple myeloma; PI= proteasome inhibitor; STD=standard deviation. a Duration from most recent prior anti-MM therapy is calculated as date of randomization - stop date of most recent anti-MM therapy +1

Approximately **75% of patients** (SVd, 75.9%; Vd, 76.8**%), had previously received a PI** with the majority receiving bortezomib (SVd, 68.7%; Vd, 70.0%). Prior lenalidomide treatment was also common (SVd, 39.5%; Vd, 37.2%). Prior high dose chemotherapy with stem cell rescue had been administered

to 39.0% and 30.4% of patients in the SVd and Vd arms, respectively. Of note, more patients in the SVd arm had received prior pomalidomide and/or daratumumab than in the Vd arm (pomalidomide, 5.6% vs 3.4% and daratumumab, 5.6% vs 2.9%, respectively).

Approximately one-third of patients had prior stem cell transplantation. Similar proportions of patients in both arms had received prior anti-MM radiotherapy (15.4% in the SVd arm, 19.8% in Vd arm) and prior anti-MM surgery (5.6% in the SVd arm, 6.8% in Vd arm).

Details on previous lines of anti-MM treatment received are presented in table 20and details on prior antineoplastic therapy refractoriness by treatment arm are presented in table 21.

Table 8: All Previous Common Lines (⩾2%) of Anti-MM Treatment Received

	SVd Arm (N=195)	**Vd Arm (N=207)**	**Total (N=402)**
Bortezomib, cyclophosphamide, dexamethasone	33(16.9)	33(15.9)	66(16.4)
Lenalidomide, dexamethasone	27(13.8)	32(15.5)	59(14.7)
Cyclophosphamide, thalidomide, dexamethasone	19(9.7)	22(10.6)	41(10.2)
Bortezomib, melphalan, prednisone/prednisolone	14(7.2)	16(7.7)	30(7.5)
Bortezomib, dexamethasone	7(3.6)	16(7.7)	23(5.7)
Bortezomib, thalidomide, dexamethasone	7(3.6)	16(7.7)	23(5.7)
Thalidomide, dexamethasone	8(4.1)	8(3.9)	16(4.0)
Melphalan, thalidomide, prednisone/prednisolone	4(2.1)	10(4.8)	14(3.5)
Carfilzomib, melphalan, prednisone/prednisolone	5(2.6)	8(3.9)	13(3.2)
Bortezomib, lenalidomide, dexamethasone	5(2.6)	5(2.4)	10(2.5)
Doxorubicin, vincristine, dexamethasone	3(1.5)	7(3.4)	10(2.5)
Lenalidomide	7(3.6)	3(1.4)	10(2.5)
Melphalan, prednisone/prednisolone	1(0.5)	9(4.3)	10(2.5)
Pomalidomide, dexamethasone	5(2.6)	3(1.4)	8(2.0)

Table 9: Prior Antineoplastic Therapy Refractoriness by Treatment Arm (All Patients in the Intent-to-Treat Population)

	SVd Arm (N = 195)	**Vd Arm (N = 207)**	**Total (N = 402)**
Number of Prior Lines of Anti-MM Therapy			
n	195	207	402
Median	1	2	2
Mean (STD)	1.7 (0.74)	1.7 (0.79)	1.7 (0.77)

	SVd Arm (N = 195)	**Vd Arm (N = 207)**	**Total (N = 402)**
Min, Max	1, 3	1, 3	1, 3
Number of Prior Lines of Anti-MM Therapy, n (%)			
1	99 (50.8)	99 (47.8)	198 (49.3)
2	65 (33.3)	64 (30.9)	129 (32.1)
3	31 (15.9)	44 (21.3)	75 (18.7)
Previously Exposed, n(%)			
Bortezomib	134 (68.7)	145 (70.0)	279 (69.4)
Carfilzomib	20 (10.3)	21 (10.1)	41 (10.2)
Ixazomib	6 (3.1)	3 (1.4)	9 (2.2)
Thalidomide	78 (40.0)	87 (42.0)	165 (41.0)
Lenalidomide	77 (39.5)	77 (37.2)	154 (38.3)
Pomalidomide	11 (5.6)	7 (3.4)	18 (4.5)
Daratumumab	11 (5.6)	6 (2.9)	17 (4.2)
PI (Bortezomib or Carfilzomib or Ixazomib)	148 (75.9)	159 (76.8)	307 (76.4)
IMiD (Thalidomide or Lenalidomide or Pomalidomide)	138 (70.8)	147 (71.0)	285 (70.9)
Refractory, n(%)			
Bortezomib	18 (9.2)	29 (14.0)	47 (11.7)
Carfilzomib	5 (2.6)	5 (2.4)	10 (2.5)
Ixazomib	2 (1.0)	1 (0.5)	3 (0.7)
Thalidomide	24 (12.3)	34 (16.4)	58 (14.4)
Lenalidomide	53 (27.2)	53 (25.6)	106 (26.4)
Pomalidomide	10 (5.1)	6 (2.9)	16 (4.0)
Daratumumab	10 (5.1)	6 (2.9)	16 (4.0)
PI (Bortezomib or Carfilzomib or Ixazomib)	24 (12.3)	34 (16.4)	58 (14.4)
IMiD (Thalidomide or Lenalidomide or Pomalidomide)	74 (37.9)	86 (41.5)	160 (39.8)

Source: CSR KCP-330-023; Updated Analysis; Table 14.4.1.1

Overall, a 34% of patients received an SCT prior to entering the BOSTON study (39% in the SvD arms and 30.4% in the Vd arm). Of note, 33% of patients were >70 years old at enrolment (at diagnosis 24%

of patients were >70 years old) and would generally not be considered for ASCT per the European Society for Medical Oncology (ESMO) guidelines.

Numbers analysed

For the BOSTON study, the intent-to-treat (ITT) population (N=402) consisted of 195 and 207 patients randomized to the SVd and Vd arms, respectively.

Three patients never received study drug in the Vd arm and were excluded from the per-protocol (PP) population.

In addition, 2 patients from the Vd arm and 1 patient from the SVd arm were excluded from the PP population due to <70% compliance of study drug (2 patients) and protocol deviation (1 patient).

Table 22. Analysis Populations

Populations	Total (N=402) n (%)
Total Randomized Patients	**402 (100.0)**
Efficacy Populations	
ITT Population	402 (100.0)
SVd Arm	195 (48.5)
Vd Arm	207 (51.5)
Per-Protocol Population	396 (98.5)
SVd Arm	194 (48.3)
Vd Arm	202 (50.2)
Safety Populations	
Total Safety Population	399 (99.3)
SVd Arm	195 (48.5)
Vd Arm	204 (50.7)
Additional Analysis Populations	
SVdX Arm[a]	63 (15.7)
SdX Arm[b]	11 (2.7)

Source: Table 14.1.1.3. SdX=selinexor plus low-dose dexamethasone treatment after crossover; SVd=selinexor plus bortezomib plus lowdose dexamethasone; SVdX=selinexor plus bortezomib plus low-dose dexamethasone treatment after crossover; Vd=bortezomib plus low-dose dexamethasone. Note: Denominator is total number of patients who were randomized. a Patients in the safety population who crossed over from the Vd arm to the SVdX treatment and have received at least 1 dose of selinexor. b Patients in the safety population who crossed over from the Vd arm to the SdX treatment and have received at least 1 dose of selinexor.

A total of **74 patients** who were originally randomized to the Vd arm experienced PD and **crossed over to SVd (n=63) or Sd (n=11) treatment.**

Outcomes and estimation

Patient response was assessed centrally by an IRC according to the IMWG response criteria for MM (Kumar 2016). The response data presented in the following sections refer to these assessments by the IRC, unless otherwise specified.

All efficacy analyses were conducted using the **ITT population**, unless otherwise specified and all tests (log-rank tests, Cochran-Mantel-Haenszel tests) were one-sided, unless otherwise stated.

Primary Efficacy Endpoint: *Progression-Free Survival*

As per the **primary analysis** the KCP-330-023 (BOSTON) study achieved its primary endpoint with a statistically significant improvement in median PFS in the SVd arm (13.93 months) compared with the Vd arm (9.46 months; p=0.0075; HR, 0.70; 95% CI: 0.5279-0.9335). This represents an increase in median PFS of more than 4.4 months (a 47% improvement) and a 30% reduction in the risk of PD or death. The PFS on the Vd control arm was similar to that reported in recent studies.

Table 23. Progression-Free Survival Based on IRC Assessment by Treatment Arm (ITT Population)

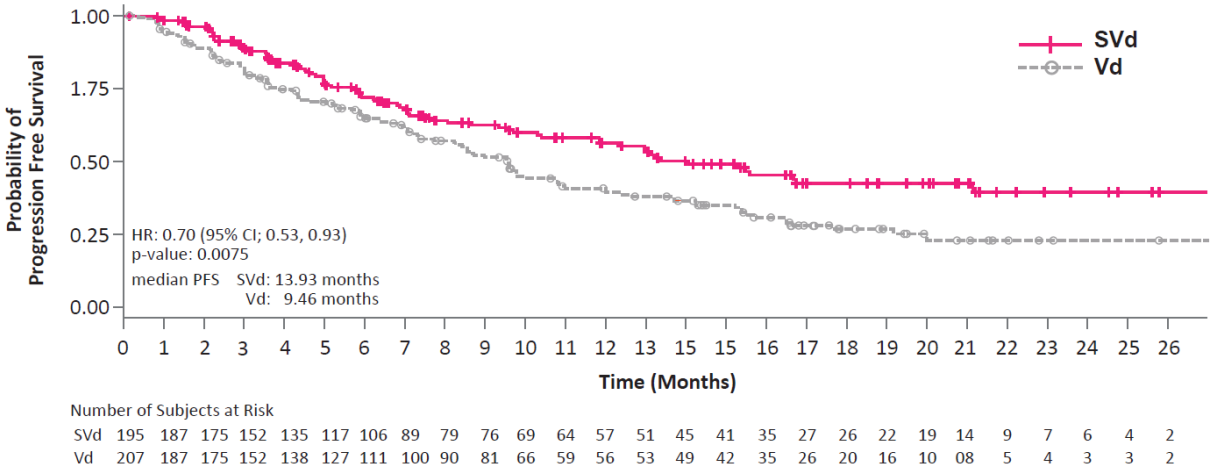
	Primary Analysis DCO date: 18 Feb 2020.		**Updated Analysis** DCO date: 15 Feb 2021	
	SVd Arm (N=195)	**Vd Arm (N=207)**	**SVd Arm (N=195)**	**Vd Arm (N=207)**
Patients with Events, n (%)	80 (41.0)	124 (59.9)	92 (47.2)	137 (66.2)
PD	69 (35.4)	111 (53.6)	79 (40.5)	122 (58.9)
Death	11 (5.6)	13 (6.3)	13 (6.7)	15 (7.2)
Patients Censored, n (%)	115 (59.0)	83 (40.1)	103 (52.8)	70 (33.8)
No Adequate Post-Baseline Response Assessment	3 (1.5)	6 (2.9)	3 (1.5)	6 (2.9)
Documented Treatment Discontinuation and Reasons	73 (37.4)	41 (19.8)	77 (39.5)	48 (23.2)
PD per Investigator Assessment	0	1 (0.5)	0	1 (0.5)
Withdrawal by Patient	35 (17.9)	16 (7.7)	35 (17.9)	19 (9.2)
Adverse Event	31 (15.9)	20 (9.7)	31 (15.9)	23 (11.1)
Physician Decision	7 (3.6)	4 (1.9)	10 (5.1)	4 (1.9)
Lost to Follow-up	2 (1.0)	2 (1.0)	1 (0.5)	1 (0.5)
Database Cut	37 (19.0)	34 (16.4)	3 (1.5)	2 (1.0)
Median Follow-up Time (Months)	13.17	16.53	20 (10.3)	14 (6.8)
95% CI	(10.64, 15.34)	(14.39, 17.71)	13.47 (10.64, 24.87)	24.48 (21.16, 29.17)
Progression-Free Survival (Months)				
Median	13.93	9.46	13.24	9.46
95% CI	(11.73, NE)	(8.11, 10.78)	(11.73, 23.43)	(8.11, 10.78)
Stratified Log-rank Test[a]				
One Sided P-value	0.0075		0.0064	
Hazard Ratio [ab]	0.7020		0.7096	
95% CI	(0.5279, 0.9335)		(0.5417, 0.9296)	
Supremum Test for Proportionals Hazards Assumption	0.6520		0.7020	

Source: Table 14.2.1.1.1.1 and Table 14.2.1.1.1.1_updated
CI=confidence interval; IRC=independent review committee; MM=multiple myeloma; NE=not evaluable; PD=progressive disease; R-ISS= Revised International Staging System; SVd=selinexor plus bortezomib plus lowdose dexamethasone; Vd=bortezomib plus low-dose dexamethasone. Note: Progression-free survival is calculated from date of randomization until the first date of IRC-confirmed PD per International Myeloma Working Group response criteria, or death due to any cause, whichever occurs first.
a Stratified for prior proteasome inhibitor therapies, number of prior anti-MM regimens and R-ISS Stage at study entry.
b Based on stratified Cox Proportional Hazard model with Efron's Method of handling ties.

Data are similar to the previously reported.

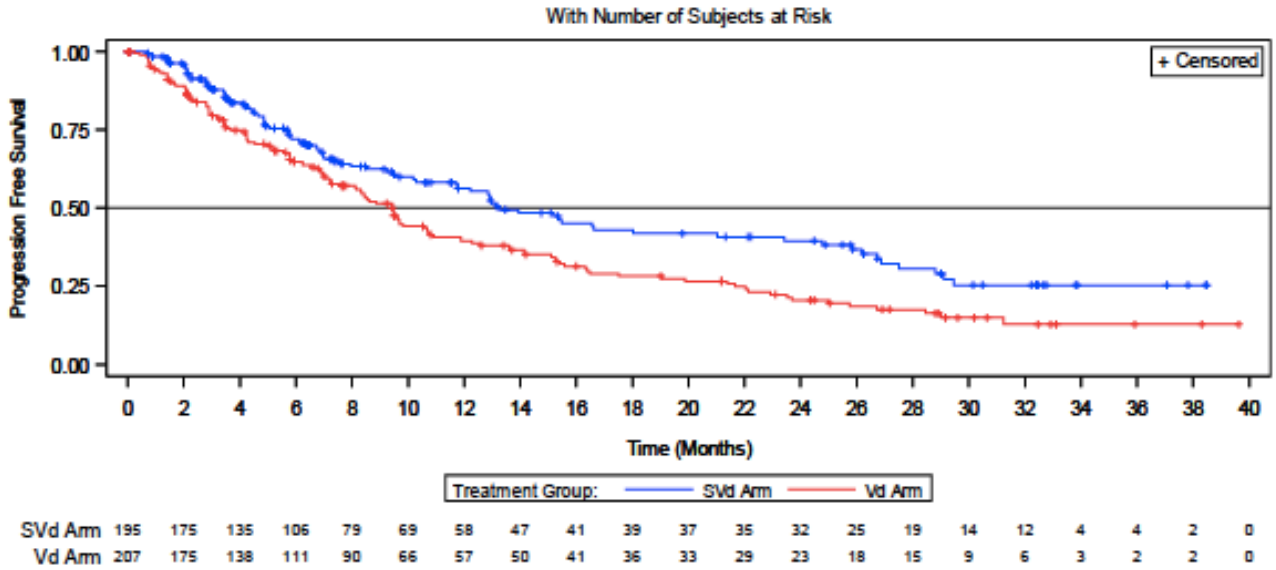
Figure 4. Kaplan-Meier Curve of Progression-free Survival by Treatment Based per IRC Assessment - Study KCP-330-023/BOSTON - ITT Population

Primary Analysis (A)



Source: Module 5.3.5.1, KCP-330-023 CSR, Figure 14.2.1.1.1.1
Data cut-off date: 18 Feb 2020.
IRC=independent review committee; SVd=selinexor plus bortezomib plus low-dose dexamethasone;
Vd=bortezomib plus low-dose dexamethasone.
Note: Progression-free survival is calculated from date of randomization until the first date of IRC-confirmed progressive disease per International Myeloma Working Group response criteria, or death due to any cause, whichever occurred first.

Updated Analysis (B)



HR=hazard ratio; PFS=progression-free survival; IRC=independent review committee; SVd=selinexor plus bortezomib plus low-dose dexamethasone; Vd=bortezomib plus low-dose dexamethasone.
Note: Progression-free survival is calculated from date of randomization until the first date of IRC-confirmed progressive disease per International Myeloma Working Group response criteria, or death due to any cause, whichever occurred first.
Data cut-off date updated: 15 February 2021

Additional Sensitivity Analyses and Supportive Analyses for primary endpoint-PFS

Modifications of the primary PFS endpoint analysis were used for sensitivity analyses.

A sensitivity analysis in which patients with PD or death after 2 or more missed visits were censored was performed, confirming the results from the primary analysis. The median PFS was 15.21 months (95%

CI: 11.76, NE) in the SVd arm and 9.46 months (95% CI: 8.11, 10.78) in the Vd arm (stratified log-rank test: p=0.0042)

Similar improvement in PFS was noted when patients were not censored at treatment discontinuation: the median PFS was 13.24 months (95% CI: 10.28, NE) in the SVd arm and 9.46 months (95% CI: 8.11, 10.78) in the Vd arm (stratified log-rank test: 0.0086).

When initiation of non-study antineoplastic therapy was also counted as an event, results similar to the results of the primary analysis were obtained: the median PFS was 13.24 months (95% CI: 10.28, NE) in the SVd arm and 9.43 months (95% CI: 7.62, 10.71) in the Vd arm (stratified log rank test: p=0.0097).

Similar results were obtained when clinical progression (i.e., PD not confirmed by IRC) was also counted as an event: the median PFS was 13.93 months (95% CI: 11.73, NE) in the SVd arm and 9.46 months (95% CI: 8.11, 10.78) in the Vd arm (stratified logrank test: p=0.0075). When the date of IRC-confirmed PD at an unscheduled visit was changed to the next scheduled visit: the median PFS was 13.40 months (95% CI: 11.76, NE) in the SVd arm and 9.46 months (95% CI: 8.21, 10.78) in the Vd arm (stratified log-rank test: p=0.0069). If the confirmation of PD was based on the Investigator's assessment instead of the IRC's assessment, the median PFS was 13.93 months (95% CI: 11.73, NE) in the SVd arm and 9.46 months (95% CI: 8.44, 11.89) in the Vd arm (stratified log-rank test: p=0.0171).

The improvement in PFS in the SVd arm was maintained during all the different sensitivity analyses. However, when treatment discontinuation for any reason was counted as a PFS event, there were no major differences between treatment arms: the median PFS was 6.70 months (95% CI: 5.75, 7.66) in the SVd arm and 6.97 months (95% CI: 5.78, 8.34) in the Vd arm (stratified log-rank test: p=0.3325).

Importantly, the ORRs for patients who discontinued without reaching a PFS event were similar to the ORR in the entire SVd arm, and higher in the SVd arm (N=78, ORR=76.9%) as compared with the Vd arm (N=49, ORR=63.3%); these differences were similar to the overall ORRs in the SVd and Vd for the entire study.

Figure 5. PFS Sensitivity Analyses

PFS analysis	Median PFS and 95% CI (Months)		Stratified Log-rank p-value
	SVd	Vd	
Primary analysis, median (months)	13. 93 (11.73, NE)	9.46 (8.11, 10.78)	0.0075
Sensitivity analyses			
Patients with PD or death after 2 or more missed visits were censored	15.21 (11.76, NE)	9.46 (8.11, 10.78)	0.0042
Initiation of non-study antineoplastic therapy counted as an event	13.24 (10.28, NE)	9.43 (7.62, 10.71)	0.0097

Source: Table 14.2.1.1.1.1, Table 14.2.1.1.1.3, Table 14.2.1.1.1.5. CI=confidence interval; NE=not evaluable; PD=progressive disease; PFS=progression-free survival; SVd=Selinexor plus bortezomib plus low-dose dexamethasone; Vd=bortezomib plus low-dose dexamethasone.

Subgroup analysis

Subgroup analyses indicated that the treatment effect on PFS was consistent regardless of age, gender, number of prior lines of anti-MM therapy, stem cell transplant, presence of a high-risk chromosomal abnormality, level of renal function, frail versus fit, and baseline ECOG PS.

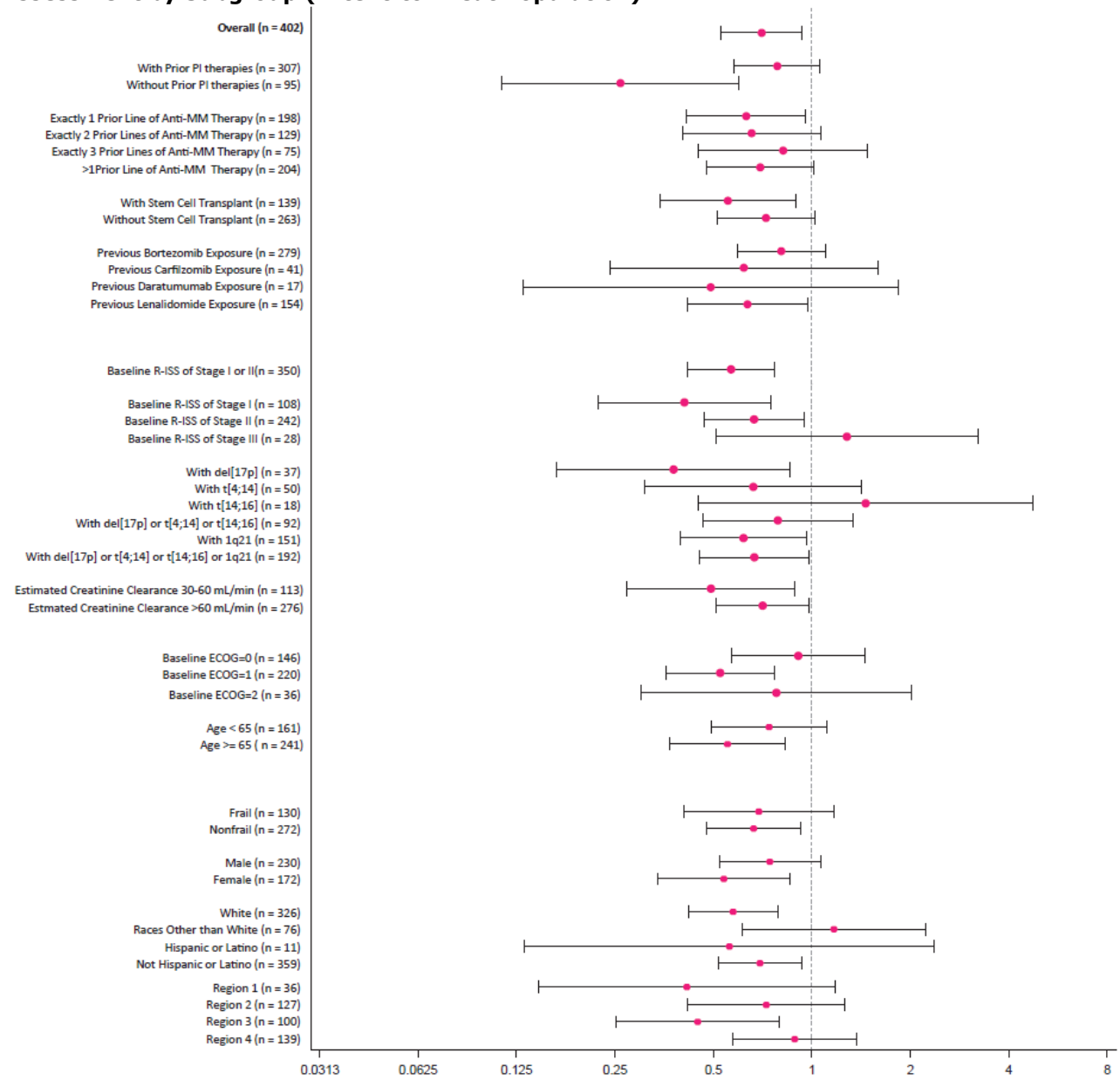
Importantly, marked differences were noted in **patients without prior PI treatment** (n=95), where there was a significant ~74% reduction (HR=0.2585; 95% CI, 0.1116-0.5988) in progression or death with SVd (median PFS not yet reached) versus Vd (median PFS: 9.69 months).

In patients with **impaired renal functio**n (creatinine clearance: 30 to 60 mL/min), the median PFS was 16.62 months (95% CI: 7.95, NE) in the SVd arm (n=53) versus 7.26 months (95% CI: 5.09, 14.13) in the Vd arm (n=60) (stratified log-rank test: p=0.0083). The hazard ratio was 0.4903 (95% CI: 0.2705, 0.8889).

The subgroup of patients with creatinine clearance of <30 mL/min was too small for a meaningful analysis (n=13 in total).

Overall, the results of the subgroup analyses suggest that the prolongations of PFS demonstrated with SVd regimen compared with Vd in the overall study population was similar in all subgroups studied.

Figure 6. Forest Plot of Hazard Ratio (SVd vs Vd) for Progression-free Survival Based on IRC Assessment by Subgroup (Intent-to-Treat Population)



Source: Figure 14.2.3.1.1.1. ECOG=Eastern Cooperative Oncology Group, MM=multiple myeloma; PI=proteasome inhibitor; R-ISS=Revised International Staging System Stage; SVd=selinexor plus bortezomib plus low-dose dexamethasone; Vd=bortezomib plus low-dose dexamethasone. Region 1: Canada, USA; Region 2: Australia, Austria, Belgium, France, Germany, Israel, Italy, Spain, UK; Region 3: Czech Republic, Greece, Hungary, Poland; Region 4: Bulgaria, India, Romania, Russian Federation, Serbia, Ukraine. Note: Please refer to Table 14.2.3.1.1.1 for exact number of hazard ratio and the 95% confidence interval. Note: Analysis based on Cox Proportional Hazard model with Efron method of handling ties.

PFS Regarding prior SCT

Median PFS (mPFS; months) based on IRC assessment in the SVd arm was similar in patients with (13.14; 95% CI: 9.59, NE) and without a prior SCT (13.24; 95% CI: 10.18, 23.43) (**Table 10**).

Table 10: PFS Based on IRC Assessment by Treatment Arm and Prior SCT (All Patients in the Intent-to-Treat Population)

	Prior SCT		**No Prior SCT**	
	SVd Arm (N = 76)	Vd Arm (N = 63)	SVd Arm (N = 119)	Vd Arm (N = 144)
Patients with Events, n(%)	33 (43.4)	39 (61.9)	59 (49.6)	98 (68.1)
PD	30 (39.5)	39 (61.9)	49 (41.2)	83 (57.6)
Death	3 (3.9)	0	10 (8.4)	15 (10.4)
PFS (Months)				
50th Percentile	13.14	9.43	13.24	9.56
95% CI	(9.59, NE)	(5.91, 10.87)	(10.18, 23.43)	(8.11, 13.60)
Log-rank Test				
1-Sided p-value	0.0074		0.0293	
Hazard Ratio (HR)	0.5645		0.7325	
95% CI	(0.3546, 0.8986)		(0.5301, 1.0121)	

Source: Table 14.4.1.3.1.

Secondary Efficacy Endpoints

Overall Response Rate

The **primary analysis** showed a higher ORR in the SVd arm than in the Vd arm based on IRC-determined ORR (i.e., the proportion of patients who achieved a partial response or better before IRC confirmed PD, initiated a new MM treatment or crossover).

The ORR was 76.4% (95% CI: 69.8, 82.2) (149 of 195 patients) in the SVd arm and 62.3% (95% CI: 55.3, 68.9) (129 of 207 patients) in the Vd arm. The stratified Cochran-Mantel-Haenszel test confirmed the statistical significance of the ORR improvement in the SVd arm over the Vd arm (odds ratio: 1.9626; 95% CI; 1.2641, 3.0471; p=0.0012).

The ≥VGPR rates were 44.6% and 32.4% (p=0.0082), and the rates of CR/sCR were 7.2%/9.7% and 4.3%/6.3% in the SVd and Vd arms, respectively (one-sided p=0.0373 for rates of CR or sCR between the SVd and Vd arms). Importantly, 9 of 33 patients with sCR or CR from the SVd arm and 8 of 22 patients with sCR or CR from the Vd arm were assessed as MRD negative.

Table 25. Overall Response Rate Based on IRC Assessment by Treatment Arm (Intent-To-Treat Population)

– Primary Analysis DCO date 18 Feb 2020

	SVd Arm (N=195)	Vd Arm (N=207)
Overall Response Rate, n(%)[a]	**149 (76.4)**	**129 (62.3)**
Exact 95% CI	(69.8, 82.2)	(55.3, 68.9)
Cochran-Mantel-Haenszel Test (SVd vs. Vd)[b]		
Odds Ratio (95% CI)	1.96 (1.26, 3.05)	
One Sided P-value	0.0012	
Breslow-Day Test for Homogeneity		
P-value	0.2430	
Best Overall Response, n(%)		
Stringent Complete Response	19 (9.7)	13 (6.3)
Exact 95% CI	(6.0, 14.8)	(3.4, 10.5)
Complete Response	14 (7.2)	9 (4.3)
Exact 95% CI	(4.0, 11.8)	(2.0, 8.1)
≥Very Good Partial Response	87 (44.6)	67 (32.4)
Exact 95% CI	(37.5, 51.9)	(26.0, 39.2)
Very Good Partial Response	54 (27.7)	45 (21.7)
Exact 95% CI	(21.5, 34.5)	(16.3, 28.0)
Partial Response	62 (31.8)	62 (30.0)
Exact 95% CI	(25.3, 38.8)	(23.8, 36.7)
Minimal Response	16 (8.2)	20 (9.7)
Exact 95% CI	(4.8, 13.0)	(6.0, 14.5)
Stable Disease	25 (12.8)	40 (19.3)
Exact 95% CI	(8.5, 18.3)	(14.2, 25.4)
PD	1 (0.5)	10 (4.8)
Exact 95% CI	(0.0, 2.8)	(2.3, 8.7)
Not Evaluable	4 (2.1)	8 (3.9)
Exact 95% CI	(0.6, 5.2)	(1.7, 7.5)
MRD negative[c]	9 (4.6)	8 (3.9)
Exact 95% CI	(2.1, 8.6)	(1.7, 7.5)

– Updated Analysis DCO date 15 Feb 2021

	SVd Arm (N=195)	Vd Arm (N=207)
Overall Response Rate, n (%)[a]	150 (76.9)	131 (63.3)
Exact 95% CI	(70.4, 82.6)	(56.3, 69.9)
Cochran-Mantel-Haenszel Test (SVd vs. Vd)[b]		
Odds Ratio (95% CI)	1.9441 (1.2468, 3.0314)	
One Sided P-value	0.0016	
Breslow-Day Test for Homogeneity		
P-value	0.4154	
Best Overall Response, n(%)		
Stringent Complete Response	19 (9.7)	13 (6.3)
Exact 95% CI	(6.0, 14.8)	(3.4, 10.5)
Complete Response	14 (7.2)	9 (4.3)
Exact 95% CI	(4.0, 11.8)	(2.0, 8.1)
Very Good Partial Response	54 (27.7)	45 (21.7)
Exact 95% CI	(21.5, 34.5)	(16.3, 28.0)
Partial Response	63 (32.3)	64 (30.9)
Exact 95% CI	(25.8, 39.4)	(24.7, 37.7)
Minimal Response	15 (7.7)	18 (8.7)
Exact 95% CI	(4.4, 12.4)	(5.2, 13.4)
Stable Disease	25 (12.8)	40 (19.3)
Exact 95% CI	(8.5, 18.3)	(14.2, 25.4)
PD	1 (0.5)	10 (4.8)
Exact 95% CI	(0.0, 2.8)	(2.3, 8.7)
Not Evaluable	4 (2.1)	8 (3.9)
Exact 95% CI	(0.6, 5.2)	(1.7, 7.5)

Source: Table 14.2.2.1.1.1 , Table 14.2.2.2.1.1 , Table 14.2.2.2.1.2 and upadted. CI=confidence interval; IRC=Independent Review Committee; MM=multiple myeloma; MRD=minimal residual disease; PI= proteasome inhibitors; R-ISS=Revised International Staging System; SVd=selinexor plus bortezomib plus low-dose dexamethasone; Vd=bortezomib plus low-dose dexamethasone. a Overall response rate is the proportion of patients who achieve a partial response or better, before IRC-confirmed PD or initiating a new MM treatment or crossover. b Analysis using Cochran-Mantel-Haenszel test stratified by prior PI therapies, number of prior anti-MM regimens, and R-ISS stage at screening. c MRD was assessed for patients who achieved CR or SCR.

Additional Sensitivity Analyses and Supportive Analyses for ORR

A sensitivity analysis that considered the patients who did not complete at least 2 scheduled post-C1D1 MM evaluations as non-responders led to similar results as the above analysis.

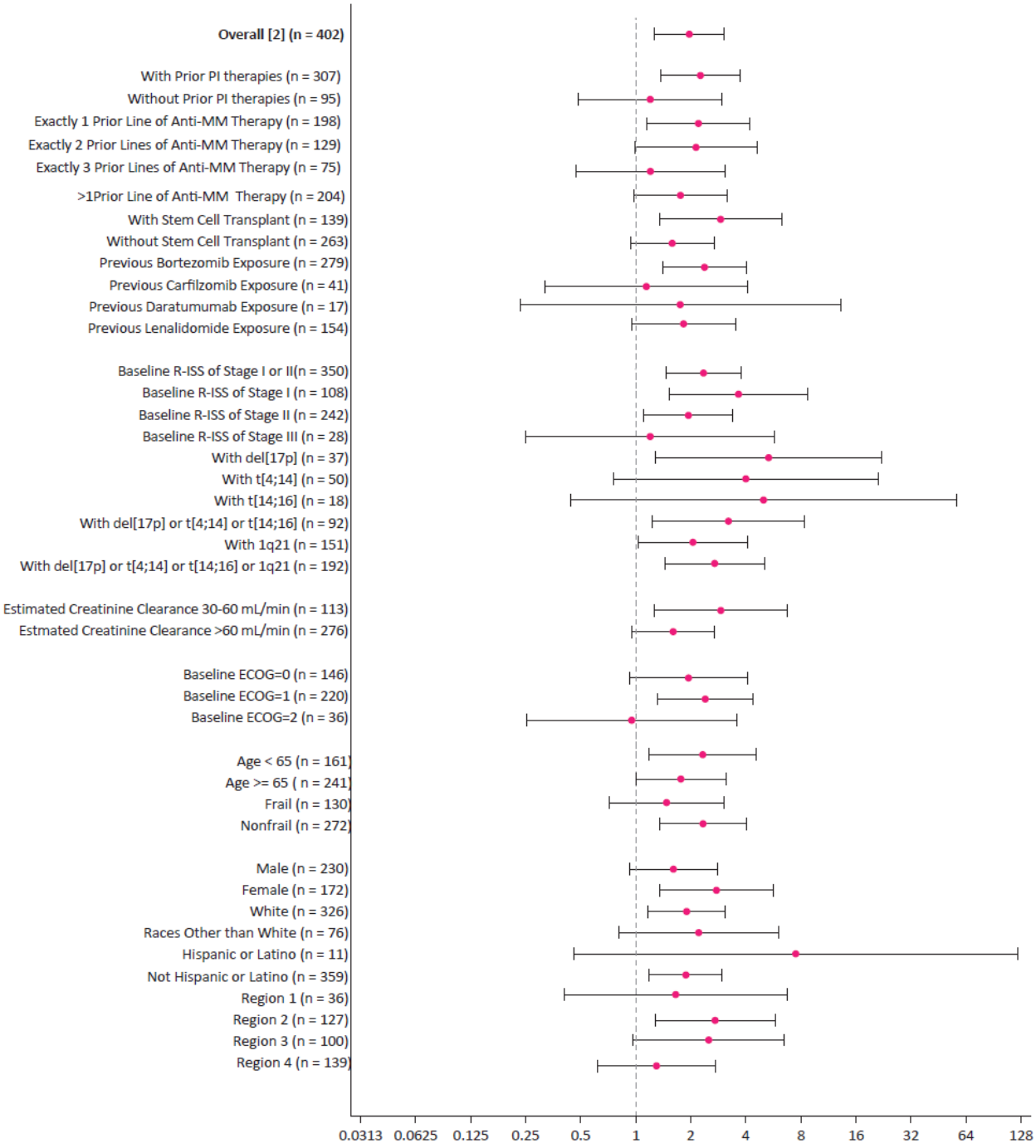
ORRs based on Investigator assessments instead of IRC assessments were also similar: the stratified Cochran-Mantel-Haenszel test showed that the ORR based on Investigator assessments was markedly higher in the SVd arm (76.9%) than in the Vd arm (63.8%) in the Vd arm (odds ratio: 1.8799; 95% CI; 1.2075, 2.9265; p=0.0023).

Of note, only 1 patient (0.5%) in the SVd arm had PD as their best response, as compared with 10 patients (4.8%) in the Vd arm.

Subgroup Analyses

Subgroup analyses demonstrate that ORR differences between the SVd arm compared to the Vd arm in the overall study population was similar in all subgroups studied.

Table 26. Forest Plot of Odds Ratio (SVd vs Vd) for Overall Response Rate Based on IRC Assessment By Subgroup (Intent To-Treat Population)



ECOG=Eastern Cooperative Oncology Group, MM=multiple myeloma; PI=proteasome inhibitor; R-ISS=The Revised International Staging System Stage; SVd=selinexor plus bortezomib plus low-dose dexamethasone; Vd=bortezomib plus low-dose dexamethasone. Note: Refer to Table 14.2.3.1.1.2 for exact number of odds ratio and the 95% confidence interval.

Rate of Very Good Partial Responses or Better Responses

In the **primary analysis**, VGPR, CR, or sCR was observed in 87 (44.6%) of 195 patients from the SVd arm and 67 (32.4%) of 207 patients from the Vd arm (odds ratio: 1.6594; 95% CI: 1.0993, 2.5049; p=0.0082; Cochran-Mantel-Haenszel test [SVd arm versus Vd arm]).

Overall, the results of the subgroup analyses suggest that the increased ≥VGPR rates demonstrated with SVd compared with Vd in the overall study population were similar in all subgroups studied.

There were no changes in the ≥VGPR rate in the **updated analysis** compared to the primary analysis. A VGPR, CR, or sCR was observed in 87 (44.6%) of 195 patients from the SVd arm and 67 (32.4%) of 207 patients from the Vd arm (odds ratio: 1.6594; 95% CI: 1.0993, 2.5049; p=0.0082; Cochran-Mantel-Haenszel test [SVd arm versus Vd arm]).

Overall Survival

Median OS was not reached for SVd at the time of the primary analysis, with 24.1% to 30.0% of death events having occurred in the SVd and Vd arms, respectively. At a **median follow-up of 17.5 months**, the median OS for patients in the Vd arm was 24.97 months (95% CI: 23.49, NE). At a **median follow-up of 17.3 months**, the median OS for patients in the SVd arm was not reached.

Seventy-four (36%) patients from the Vd arm crossed over after confirmed PD to receive a regimen that included selinexor (SVdX or SdX).

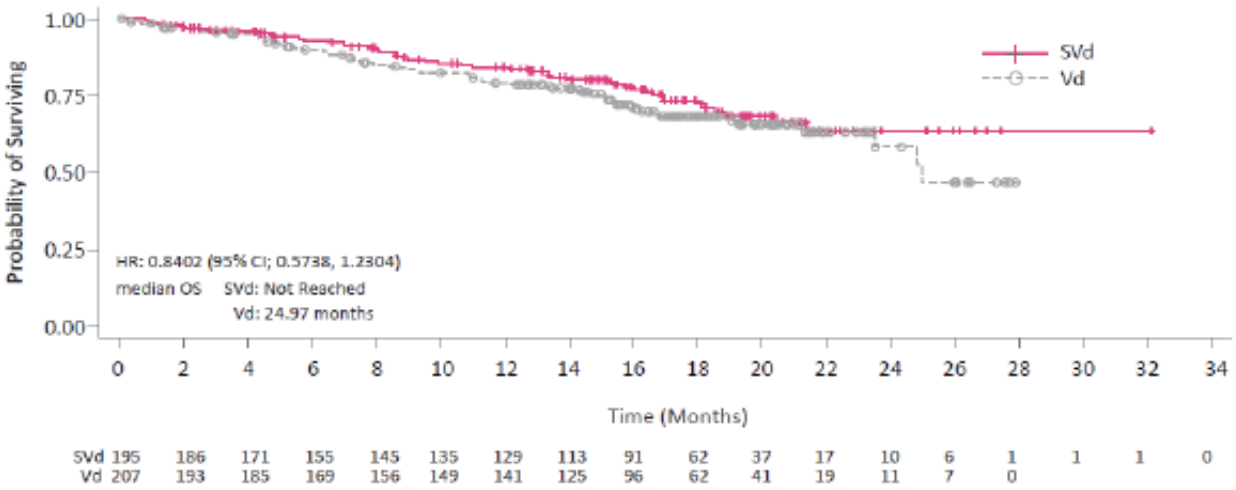
Table 27. Overall Survival by Treatment Arm (Intent-To-Treat Population)

	– Primary Analysis – (DCOD 18 Feb 2020)		– Updated Analysis (DCOD 15 Feb 2021)	
Patients with Events, n (%)	**SVd Arm (N=195)**	**Vd Arm (N=207)**	**SVd Arm (N=195)**	**Vd Arm (N=207)**
Death	47 (24.1)	62 (30.0)	68 (34.9)	80 (38.6)
Patients Censored, n (%)	148 (75.9)	145 (70.0)	127 (65.1)	127 (61.4)
Study Discontinuation due to	39 (20.0)	38 (18.4)	42 (21.5)	42 (20.3)
Patient Withdrawal	37 (19.0)	37 (17.9)	39 (20.0)	41 (19.8)
Other	2 (1.0)	1 (0.5)	3 (1.5)	1 (0.5)
Lost to Follow-up	7 (3.6)	6 (2.9)	12 (6.2)	7 (3.4)
Database Cut	102 (52.3)	101 (48.8)	73 (37.4)	78 (37.7)
Median Follow-up Time (Months)	17.28	17.51	28.71	28.65
95% CI	(16.56, 18.27)	(17.08, 18.23)	(27.24, 29.90)	(27.63, 29.67)
Overall Survival (Months)				
Median	NE	24.97	36.67	32.76
95% CI	(NE, NE)	(23.49, NE)	(30.19, NE)	(27.83, NE)
Stratified log-rank test[a]				
One Sided P-value	0.1852		0.2152	
Hazard Ratio [a,b]	0.84		0.8764	
95% CI	(0.57, 1.23)		(0.6313, 1.2168)	
Supremum Test for Proportionals Hazards Assumption	0.8330		0.8350	

Source: Table 14.2.2.3.1.1, Table 14.2.2.3.1.2 and _updated..CI=confidence interval; MM=multiple myeloma; NE=not evaluable; PI=proteasome inhibitors; R-ISS=Revised International Staging System; SVd=selinexor plus bortezomib plus low-dose dexamethasone; Vd=bortezomib plus low-dose dexamethasone. Note: Overall survival is calculated from date of randomization to date of death. Patients without events were censored at the date of study discontinuation or date of last participating visit, whichever occurred first. a Stratified for prior PI therapies, number of prior anti-MM regimens and R-ISS Stage at screening. b Based on stratified Cox Proportional Hazard model with Efron's Method of handling ties.

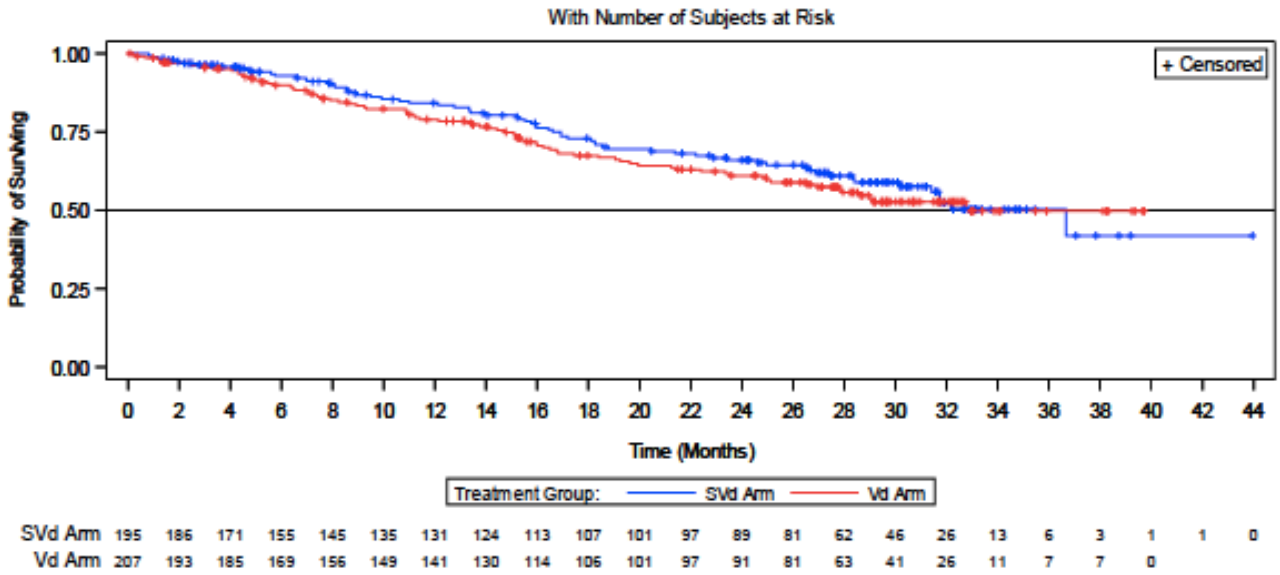
Figure 7. Kaplan-Meier Curve of Overall Survival by Treatment Arm (Intent-to-Treat Population)

– Primary Analysis



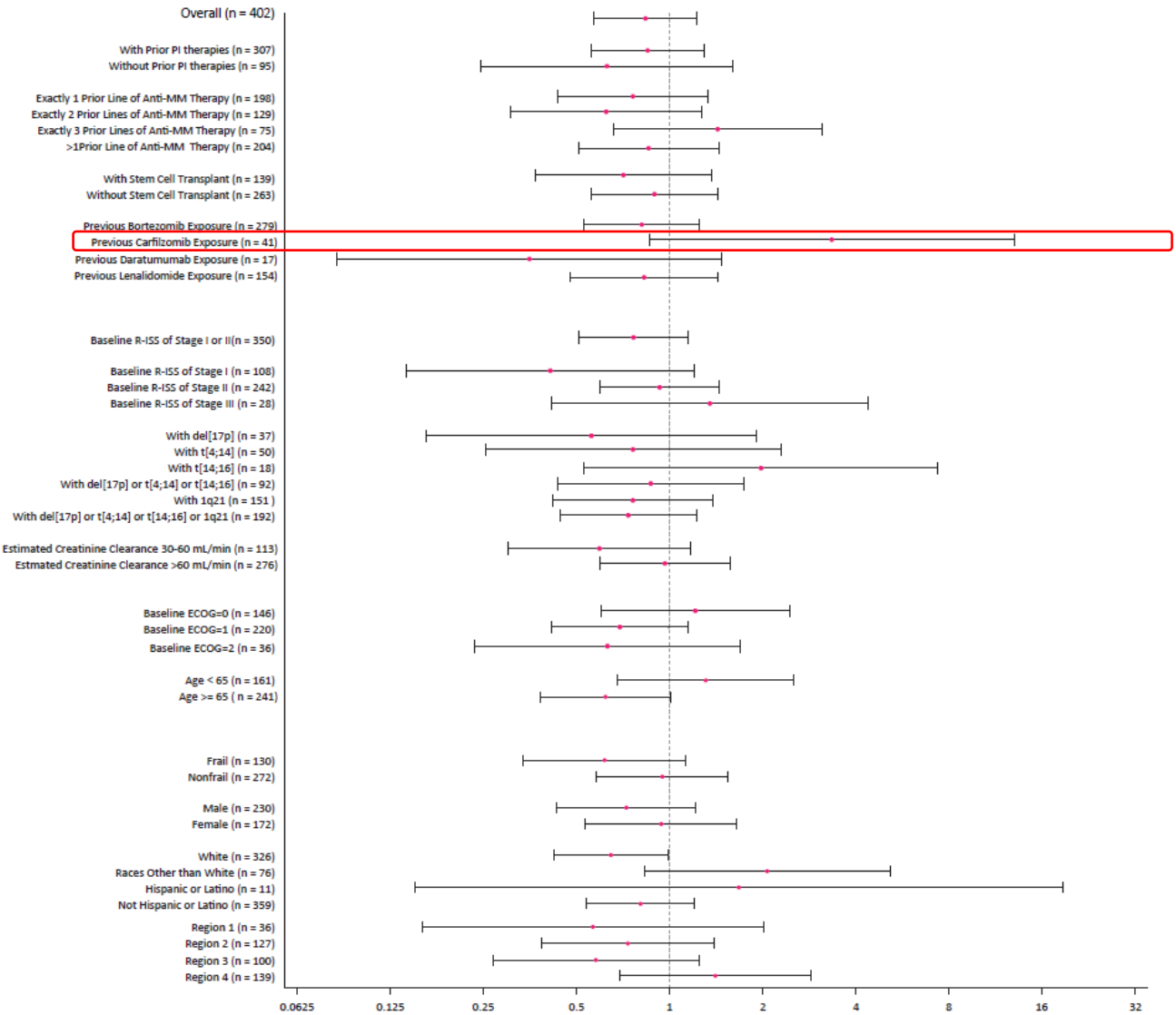
Source: Figure 14.2.2.3.1.1.

– Updated Analysis



Source: Figure 14.2.2.3.1.1_updated. Data cut-off date: 15 Feb 2021. CI=confidence interval; mOS=median overall survival; SVd=selinexor plus bortezomib plus low-dose dexamethasone; Vd=bortezomib plus low-dose dexamethasone. Note: Overall survival was calculated from date of randomization to date of death. Patients without events were censored at the date of study discontinuation or date of last participating visit, whichever occurred first.

Figure 8. Forest Plot of Overall Survival Hazard Ratios (Intent-to-Treat Population)



Source: Figure 14.2.3.1.1.4. Data cut-off date: 18 Feb 2020. MM=multiple myeloma; PI=proteasome inhibitor; R-ISS: The Revised International Staging System Stage;SVd=selinexor plus bortezomib plus low-dose dexamethasone; Vd=bortezomib plus low-dose dexamethasone.Note: Please refer to Table 14.2.3.1.1.4 for exact number of hazard ratio and the 95% confidence interval.

With a longer follow-up, at the time of the updated analysis (15 Feb 2021), the median OS was 36.67 (95% CI: 30.19, NE) months in the SVd arm and 32.76 (95 CI: 27.83, NE) months in the Vd arm, what is translated to a median improvement of approximately 4 months in patients treated with selinexor.

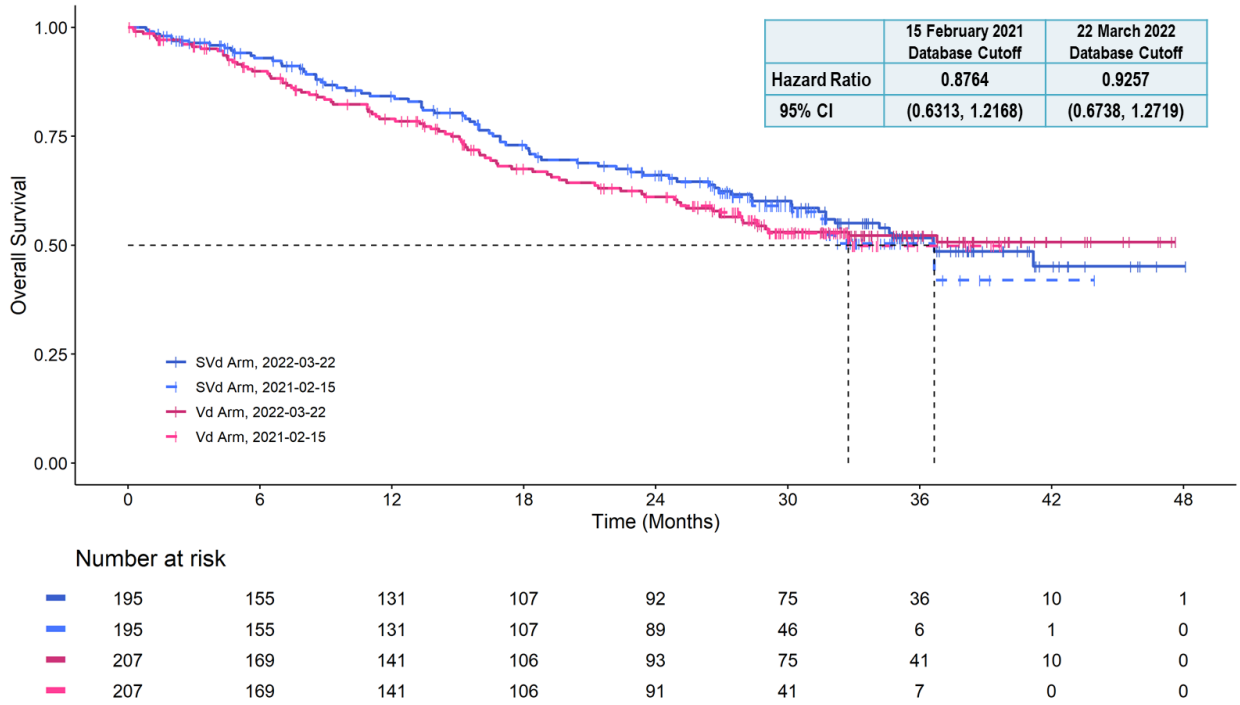
Futher updated OS data, with a data cut-off of 22 March 2022, were provided. As of 22 March 2022, there were a total of 74 (37.9%) and 83 (40.1%) deaths in the SVd and Vd arms, respectively. Based on these data, OS was overall consistent with the previous data cut and there was no detrimental effect of SVd in terms of OS. Bearing in mind that cross-over was allowed in the BOSTON study,a 2-stage estimation method accounting for cross-over effect on OS was conducted with the 22 March 2022 data cut, reporting a switch-adjusted HR for OS of 0.88 (95%C CI: 0.64, 1.22).

Overall Survival By Treatment Arm - Intent-To-Treat Population (22 March 2022)

	SVd Arm (N = 195)	Vd Arm (N = 207)
Patients with Events, n(%)		
Death	74 (37.9)	83 (40.1)
Patients Censored, n(%)	121 (62.1)	124 (59.9)
Study Discontinuation due to	107 (54.9)	115 (55.6)
Patient Withdrawal	39 (20.0)	43 (20.8)
Other	68 (34.9)	72 (34.8)
Lost to Follow-up	13 (6.7)	8 (3.9)
Database Cut	1 (0.5)	1 (0.5)
Median Follow-up Time (Months)	33.61	33.84
95% CI	(32.26, 35.19)	(32.92, 35.71)
Overall Survival (Months)		
25th Percentile	16.59	14.72
95% CI	(13.93, 22.87)	(11.10, 17.45)
50th Percentile	36.67	NE
95% CI	(31.74, NE)	(26.91, NE)
75th Percentile	NE	NE
95% CI	(NE, NE)	(NE, NE)
Stratified log-rank test [1]		
One Sided P-value	0.3167	
Hazard Ratio [1] [2]	0.9257	
95% CI	(0.6738, 1.2719)	
Supremum Test for Proportionals Hazards Assumption	0.6120	

(Database Cutoff Date: 2022-03-22)
CI=Confidence Interval.
Note: Overall survival is calculated from date of randomization to date of death. Patients without events were censored at the date of study discontinuation or date of last participating visit, whichever occurred first.
[1] Stratified for prior PI therapies, number of prior anti-MM regimens and R-ISS Stage at screening.
[2] Based on stratified Cox Proportional Hazard model with Efron's Method of handling ties.

Figure 9: Kaplan-Meier Curve of Overall Survival by Treatment Arm for the Intent-to-Treat Population (15 February 2021 and 22 March 2022)



Overall Survival Sensitivity Analysis

Of the 207 Vd-treated patients in the ITT population, 111 (53.6%) patients had PD.

Of these patients who had PD, 74 (66.7%) patients crossed over to SVdX or SdX.

The median duration from PD to cross over was 43 days with 97.3% switching within 4 months. A switch-adjusted HR based on the two-stage estimation method (Latimer 2017, Latimer 2018) comparing overall survival on SVd versus Vd at any point in the study was 0.77 (95% CI: 0.52, 1.14). On average, treatment with SVd over the trial produced an estimated approximately 23% lower risk of death. The 27-month survival rate based on Kaplan-Meier estimates was 45% and 63% for the Vd arm and SVd arm, respectively.

The two-stage estimation method proceeded by using the PD time point as a secondary baseline for all Vd-treated patients and comparing post-progression survival in the Vd arm switchers and non-switchers based on a Weibull accelerated failure time model, adjusting for prognostic characteristics measured at baseline and the time of PD. The accelerated failure time model adjusted for age at enrollment (centered at the mean), number of ongoing medical history terms, number of adverse events of special interest, R-ISS stage, time of progression, physician experience with SVd (measured with number of SVd patient in a site), ECOG score, prior exposure, sensory component of EORTC QLQ-CIPN20, and number of prior anti-MM regimens. The acceleration factor from this model was used to adjust the observed survival times in Vdswitching patients to obtain counterfactual survival times.

A Cox proportional hazards regression model (stratified by R-ISS stage, prior PI therapy, and number of prior anti-MM regimens) was then fitted to the observed SVd arm survival times and the counterfactual Vd arm survival times to estimate a treatment switch-adjusted HR. The standard error of the log HR estimates was obtained from 2,000 bootstrap samples; hence, CI and p-value were based on a t-distribution using normal distribution theory method with the bootstrapped standard error. The possible artificial reduction of survival times when the goal of treatment is to extend survival times precluded re-

censoring in the sensitivity analysis using a two-stage estimation method. Likewise, beside the relatively small number of deaths and sample size, the artificial censoring of death when deaths are, in fact, known to have occurred favored a two-stage estimation method over inverse probability of censoring weight (IPCW; Robins 2000, Herman 2001) in the present context.

A switch-adjusted HR based on IPCW with weights trimmed at the 99th percentile was 0.86 (95% CI: 0.53, 1.40). The variables included in the model for IPCW were selected to cover domains of disease stage, functions, and tolerability.

OS in patients with prior SCT

Median OS (mOS; months) in the SVd arm was not significantly different in patients with a prior SCT (36.67; 95% CI: 31.74, NE) than those without a prior SCT (31.41; 95% CI: 26.68, NE) (table 28).

Table 28: Overall Survival by Treatment Arm and Prior SCT (All Patients in the Intent-to-Treat Population)

	Prior SCT		**No Prior SCT**	
	SVd Arm (N = 76)	Vd Arm (N = 63)	SVd Arm (N = 119)	Vd Arm (N = 144)
Patients with Events, n(%)				
Death	25 (32.9)	22 (34.9)	43 (36.1)	58 (40.3)
Overall Survival (Months)				
50th Percentile	36.67	NE	31.41	32.76
95% CI	(31.74, NE)	(24.84, NE)	(26.68, NE)	(26.58, NE)
Log-rank Test				
1-Sided p-value	0.2777		0.3842	
Hazard Ratio (HR)	0.8421		0.9427	
95% CI	(0.4745, 1.4942)		(0.6354, 1.3987)	

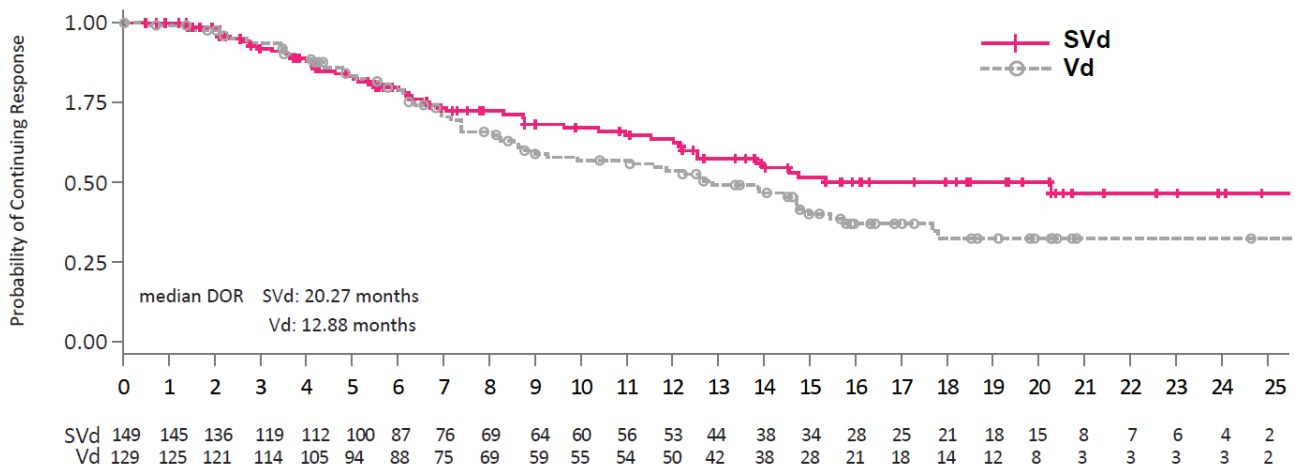
Source: Table 14.4.1.3.2

Duration of Response

The **median DOR** in patients with confirmed PR or better (i.e., the duration of the time interval between the first IRC-confirmed PR or better response and the first IRC-confirmed PD or death due to any cause, whichever occurred first), was **20.3 months** (95% CI: 12.55, NE) in the SVd arm and **12.9 months** (95% CI: 9.26, 15.77) in the Vd arm (p=0.1364, stratified log-rank test)

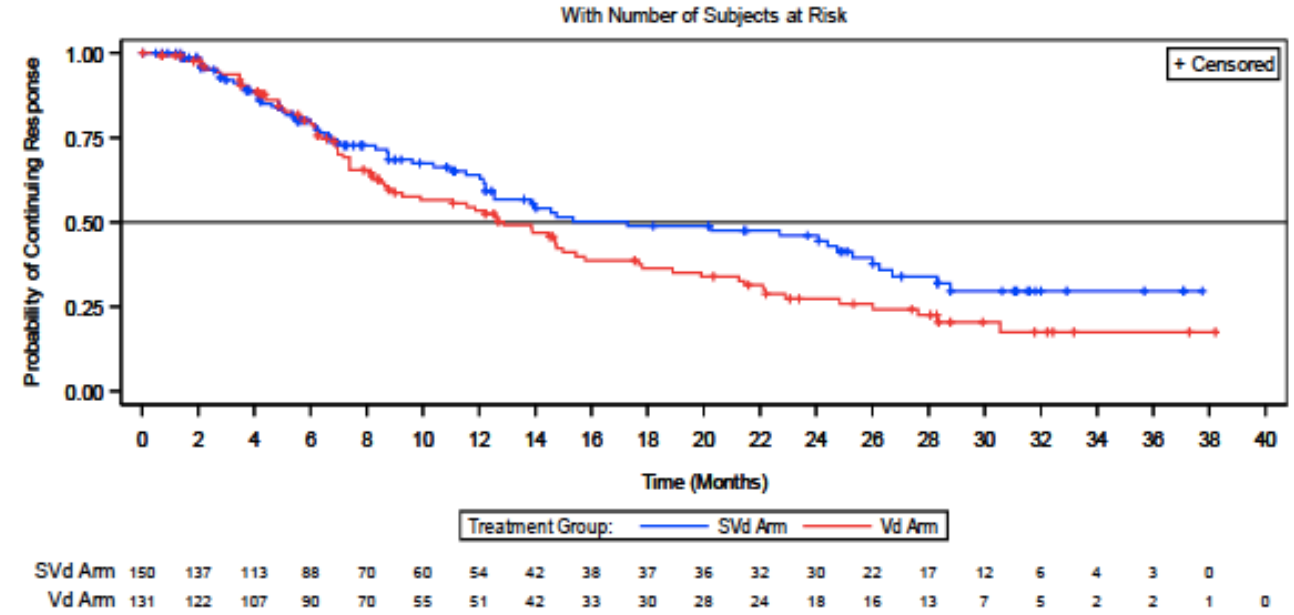
Figure 10. Kaplan-Meier Curves of Duration of Response by Treatment Arm (Intent-to- Treat Population)

– Primary Analysis



Source: Figure 14.2.2.4.1.1, Table 14.2.2.4.2.1. Data cut-off date: 18 Feb 2020.

– Updated Analysis



Source: Figure 14.2.2.4.1.1_updated. Data cut-off date: 15 Feb 2021.
SVd=selinexor plus bortezomib plus low-dose dexamethasone; Vd=bortezomib plus low-dose dexamethasone. Note: Duration of response (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 occurred first.

With a longer follow-up (updated analysis), the SVd arm continued to have a longer DOR compared to Vd arm. The median DOR in patients with confirmed PR or better, was **17.3 months** (95% CI: 12.55, 26.25) in the SVd arm and **12.9 months** (95% CI: 9.26, 15.77) in the Vd arm (p=0.1103, stratified log-rank test).

Time to Next Treatment

A total of 69 (35.4%) patients in the SVd arm and 116 (56.0%) patients in the Vd arm received a new anti-MM treatment.

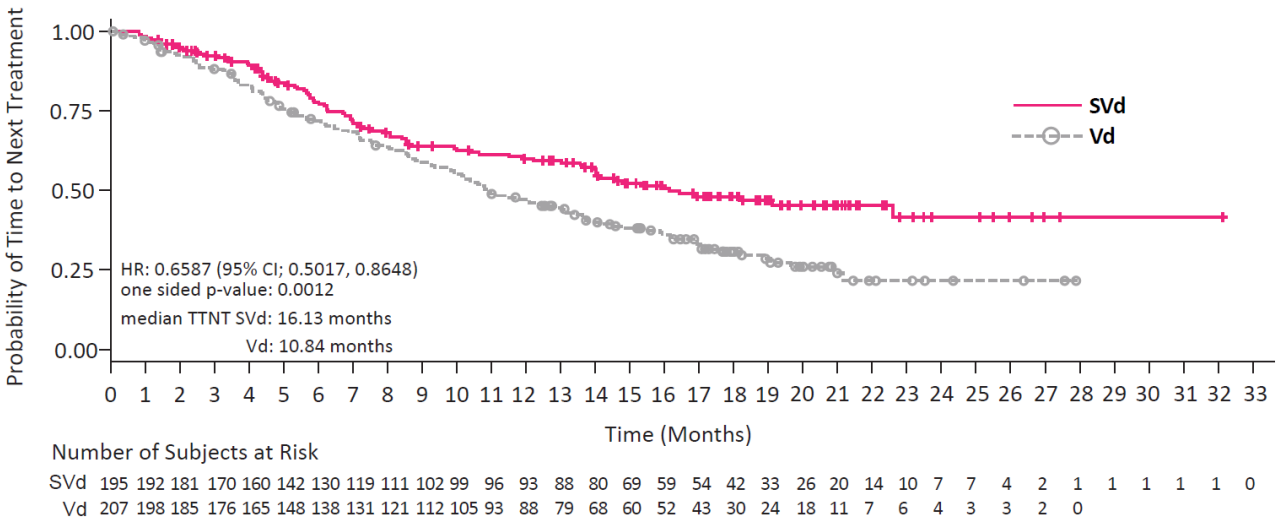
The median TTNT (time between randomization and start of next anti-MM treatment or death) was **16.13 months** in the SVd arm, which was markedly longer than the **10.84 months** in the Vd arm (p=0.0012, stratified log-rank test.

Table 29. Time to Next Treatment by Treatment Arm (Intent-To-Treat Population)

	SVd Arm (N=195)	Vd Arm (N=207)
Patients with Events, n (%)	**88 (45.1)**	**135 (65.2)**
New MM Treatment	69 (35.4)	116 (56.0)
Death	19 (9.7)	19 (9.2)
Patients Censored, n (%)	**107 (54.9)**	**72 (34.8)**
Study Discontinuation due to	32 (16.4)	21 (10.1)
Patient Withdrawal	31 (15.9)	20 (9.7)
Other	1 (0.5)	1 (0.5)
Lost to Follow-up	7 (3.6)	5 (2.4)
Database Cut	68 (34.9)	46 (22.2)
Time to Next Treatment (Months)		
Median	16.13	10.84
95% CI	(13.93, NE)	(9.82, 13.40)
Stratified log-rank test[a]		
One Sided P-value	0.0012	
Hazard Ratio [a,b]	**0.6587**	
95% CI	(0.5017, 0.8648)	
Supremum Test for Proportionals Hazards Assumption	0.0640	
Treatment-free Interval for Patients with New MM Treatment (Days)		
N	69	116
Median	28.0	14.0
Min, Max	1, 447	1, 419

Source: Table 14.2.2.7.1.1.CI=confidence interval; MM=multiple myeloma; NE=not evaluable; R-ISS=Revised International Staging System; SVd=selinexor plus bortezomib plus low-dose dexamethasone; Vd=bortezomib plus low-dose dexamethasone. Note: Time to next treatment was calculated from the date of randomization to the start of next anti-MM treatment or death, whichever occurred first. Patients without an event were censored at the date of discontinuation from the study or last participating visit or database cut-off date, whichever occurred first. a Stratified for prior PI therapies, number of prior of anti-MM regimens and R-ISS Stage at screening. ,b Based on stratified Cox Proportional Hazard model with Efron's Method of handling ties

Table 30. Kaplan-Meier Curve of Time to Next Treatment by Treatment; Study KCP-330-023/BOSTON, ITT Population-Primary Analysis



Source: KCP-330-023 CSR, Figure 14.2.2.7.1.1.
HR=hazard ratio; MM=multiple myeloma; SVd=selinexor plus bortezomib plus low-dose dexamethasone; TTNT= time to next treatment; Vd=bortezomib plus low-dose dexamethasone.
Note: Time to Next Treatment (TTNT) was calculated from the date of randomization to the start of next anti-MM treatment or death, whichever occurred first. Patients without an event is censored at the date of discontinuation from the study or last participating visit or database cutoff date, whichever occurred first.

Time to Response

The median TTR was shorter in the SVd arm than in the Vd arm (1.41 versus 1.61 months, respectively; p<0.0001, stratified log-rank test).

Table 31. Time to Response by Treatment Arm (Intent-To-Treat Population)

	SVd Arm (N=195)	Vd Arm (N=207)
Patients with an IRC-confirmed PR or Better, n(%)	**149 (76.4)**	**129 (62.3)**
Time to Partial Response or Better (Months)		
Median	1.1	1.4
Min, Max	1, 5	0, 13
Patients Censored, n(%)	**46 (23.6)**	**78 (37.7)**
Time to Response (Months)		
Median	1.41	1.61
95% CI	(1.35, 1.51)	(1.51, 2.14)
Stratified log-rank test[a]		
One Sided P-value	<0.0001	
Hazard Ratio [a,b]	**1.6712**	
95% CI	(1.3064, 2.1379)	
Supremum Test for Proportionals Hazards Assumption	0.3280	

Source: Table 14.2.2.8.1.1. CI=confidence interval; IRC=independent review committee; MM=multiple myeloma; PD=progressive disease; PI=proteasome inhibitors; PR=partial response; R-ISS=Revised International Staging System;

SVd=selinexor plus bortezomib plus low-dose dexamethasone; Vd=bortezomib plus low-dose dexamethasone. Note: Time to Response (TTR) is calculated from the date of randomization to the date of first IRC-confirmed PR or better before IRC-confirmed PD or initiating a new MM treatment or crossover. Patients without an event are censored at the last disease assessment.
a Stratified for prior PI therapies, number of prior of anti-MM regimens and R-ISS Stage at screening. b Based on stratified Cox Proportional Hazard model with Efron's Method of handling ties.

Quality of Life-Primary Analysis

For the primary analysis, patient-reported PN was assessed using the EORTC-QLQ-CIPN20 tool. Baseline CIPN20 severity was similar between the SVd and Vd arms in the ITT population on the sensory, motor, and autonomic symptom scales. Over the course of the study, a lower rate of change from baseline score was observed in the SVd arm compared with the Vd arm for the sensory scale (p=0.0038, indicating a lower sensory symptom burden) while scores were similar in both arms for the motor and autonomic scales.

For sensory PN, patients in the Vd arm consistently showed higher symptom scores compared with patients in the SVd arm. These differences were most pronounced during the first 169 days of the study when patients in the Vd arm were receiving BIW bortezomib compared with QW in the SVd arm. Similarly, based on the analysis of covariance model (adjusted for prior PI therapies, number of prior anti-MM regimens, R-ISS stage at screening, and baseline value of the subscale score), the adjusted mean change from baseline in EORTC QLQ CIPN20 scores at the target day (Day 106) was significantly lower in the SVd arm than in the Vd arm for sensory symptom scores (estimated mean treatment difference: 3.56; 95% CI: 6.99, 0.12; p=0.0423).

Health-related QoL domains of the EORTC-QLQ-C30 were included as exploratory analyses. At baseline, the measures were similar across the SVd and Vd arms. Over time, scores of the cognitive domain were lower for the SVd arm than the Vd arm (indicating worse functioning) whereas scores in the SVd arm were higher for the social domain (indicating improved functioning) while no major differences were observed for other functional domains.

For the symptom domains of the EORTC-QLQ-C30, over time, scores in the SVd arm were higher (indicating worse symptoms) compared with the Vd arm for nausea/vomiting and decreased appetite. While fatigue scores in the SVd and Vd arms were similar for the first 3 months of treatment, scores trended higher (indicating worse symptoms) in the SVd arm over subsequent cycles of treatment. Constipation scores for the SVd arm were also higher (indicating worse symptoms) compared with the Vd arm during the majority of the study. However, pain scores in the SVd arm were lower (indicating improved symptoms) compared with the Vd arm over the course of the study.

The initial reductions in pain scores observed during the first 60 days of the study (in both arms) are likely due to control of MM; this effect persisted in the SVd arm during the course of the study. No major differences were observed for other symptom domains.

Response in Patients with Cytogenetic Abnormalities

Nearly half of the patients had high-risk cytogenetic abnormalities; 97 patients (49.7%) in the SVd arm and 95 patients (45.9%) in the Vd arm.

The median PFS in patients with any high-risk cytogenetic abnormality was 12.91 months on SVd versus 8.15 months on Vd (one-sided p-value=0.0192). Similarly, the ORRs were 77.3% and 55.8%, respectively. The median OS was not reached for the SVd arm and was 23.5 months for the Vd arm.

Among patients with del[17p], the median PFS was 12.22 months (95% CI: 5.62, NE) in the SVd arm (n=21) compared to 5.91 months (95% CI: 2.04, 11.89) in the Vd arm (n=16), for a HR of 0.3762 (one-sided p-value=0.0080).

Ancillary analyses

Subgroup and sensitivity analysis have been described above.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 32. Summary of Efficacy for trial KCP-330-023 (BOSTON Study)

Title: **A phase 3 randomized, controlled, open-label study of selinexor, bortezomib, and dexamethasone (SVd) versus bortezomib and dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma (RRMM)**		
Study identifier	KCP-330-023/ BOSTON EudraCT: 2016-003957-14	
Design	The BOSTON study is a Phase 3, 2-arm, global, randomized, active comparator-controlled, open-label, multicenter study which compared the efficacy, safety and Health Related-Quality of Life of SVd versus Vd in adult patients with RRMM who had received 1 to 3 prior anti-MM regimens. Patients were randomized in a 1:1 allocation, as follows: • SVd arm: selinexor (QW) + SC bortezomib (QW) + dexamethasone. • Vd arm: SC bortezomib (Cycles 1-8 BIW, Cycles ≥9 QW) dexamethasone. Randomization was stratified based on: • Prior PI therapies (Yes or No). • Number of prior anti-MM regimens (1 versus >1). • Revised International Staging System (R-ISS) stage at study entry based on screening results (R-ISS Stage III versus R-ISS Stage I or II) (Palumbo 2016). Following confirmation of PD by the IRC, patients who received Vd were allowed to cross over to receive either SVd (i.e., the SVdX treatment arm) or selinexor + low-dose dexamethasone (i.e., the SdX treatment arm) for those patients who developed intolerance to bortezomib.	
	Duration of main phase:	Study treatment (SVd, Vd, or crossover) was continued until PD was confirmed by the IRC, Investigator or patient decision to discontinue study treatment, pregnancy, unacceptable adverse events (AEs) or toxicity that could not be managed by supportive care, withdrawal of consent, death, or Sponsor decision to terminate the study.
	Duration of Run-in phase:	not applicable

	Duration of Extension phase: Initiation of the study: First patient enrolled: First patient dosed: Last patient enrolled: Last patient dosed: Last patient last visit:		not applicable December 2016 05-June-2017 07–June-2017 31-Jan-2019 05-Feb-2019 Patients still on treatment as of June 2021
Hypothesis	Hypothesis testing will be used for the primary efficacy endpoint and for selected secondary efficacy endpoints in order **to evaluate the superiority** of SVd compared with Vd. No formal hypothesis testing will be used for other study data, such as demographics and safety data.		
Treatments groups	SVd arm: selinexor + bortezomib (QW) + dexamethasone		Selinexor will be given as a fixed oral 100 mg dose on Days 1, 8, 15, 22, and 29 of each 35-day cycle. ▪ Bortezomib will be given at a dose of 1.3 mg/m^2 SC on Days 1, 8, 15, and 22 of each 35-day cycle. ▪ Dexamethasone will be given as an oral 20 mg dose on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle.
	Vd arm: bortezomib (Cycles 1-8 BIW, Cycles ≥9 [QW]) + dexamethasone		**Cycles 1 through 8** (3-week [21-day] cycle) ▪ Bortezomib will be given at a dose of 1.3 mg/m^2 SC on Days 1, 4, 8, and 11 of each 21-day cycle. ▪ Dexamethasone will be given as an oral 20-mg dose on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle. **Cycles ≥ 9 (**5-week [35-day] cycle) ▪ Bortezomib will be given at a dose of 1.3 mg/m^2 SC on Days 1, 8, 15, and 22 of each 35-day cycle. ▪ Dexamethasone will be given as an oral 20 mg dose on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle.
	SVdX arm selinexor + bortezomib (QW) + dexamethasone		Crossover patients return to Cycle 1 for SVd treatment
	SdX Selinexor (QW) + dexamethasone		Selinexor will be given as a fixed oral 100 mg dose on Days 1, 8, 15, 22, and 29 of each 35-day cycle. ▪ Dexamethasone will be given as an oral 20 mg dose on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle.
Endpoints and definitions	Primary endpoint	Progression Free Survival (PFS)	Defined as time from date of randomization until the first date of PD, per IMWG response criteria, or death due to any cause, whichever occurs first. For the purposes of PFS determination, PD will be determined by the IRC.

	Secondary endpoint	Overall Response Rate (ORR)	Defined as any response ≥ PR based on the IRC's response outcome assessments, according to the IMWG response criteria. All changes in MM disease assessments will be based on baseline MM disease assessments prior randomization.
		Response rates for responses ≥ VGPR	Response rates at any time prior to PD or death due to any cause, for responses ≥ VGPR,
		Overall Survival (OS)	OS, defined as time to death or lost to follow-up, measured from the date of randomization until death due to any cause or until lost to follow-up, for all patients
		Duration of Response (DOR)	DOR, defined as the duration of time from first occurrence of response ≥ PR until the first date of PD or death, whichever occurs first
Database lock (cut-off)	18-Feb-2020		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The ITT population consisted of all patients who are randomized to study treatment, regardless of whether or not they receive study treatment. The ITT population included patients who have discontinued study treatment due to toxicity or PD and patients who have died from any cause. This population has been used for primary analyses of efficacy. Patients were analyzed in the treatment arm to which they were randomized and strata assignment at the time of randomization		
Effect estimate per comparison statistics and estimate variability	Treatment group	SVd	Vd
	Number of patients	n=195	n=207
	Progression Free Survival (PFS) Hazard Ratio (95% CI) One-sided p-value	0.70 (0.53, 0.93) 0.0075	
	Median PFS in months (95% CI)	13.9 (11.7, Not Reached)	9.5 (8.1, 10.8)
	Overall Response rate (ORR), n%	149 (76.4)	129 (62.3)
	95% CI One-sided p-value sCR CR VGPR PR	(69.8, 82.2) 0.0012 19 (10) 14 (7) 54 (28) 62 (32)	(55.3, 68.9) 0.0012 13 (6) 9 (4) 45 (22) 62 (30)
	≥ VGPR Response Rate, n(%) 95% CI One-sided p-value	87 (44.6) (37.5, 51.9) 0.0082	67 (32.4) (26.0, 39.2) 0.0082

	DoR Median months 95% CI	20.3 (12.55, NE)	12.9 (9.26, 15.77)
	OS n (%) Median months 95% CI	Not Reached (Not Reached, Not Reached)	24.97 (23.49, Not Reached)
Notes			

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

Table 33: Number of Subjects by Age Group in Controlled and Non-Controlled Trials

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85 + (Older subjects number /total number)**
Controlled Trials (KCP-330-023 only)	160/402	78/402	3/402
Non Controlled Trials (KCP-330-017 only)	19/42	1/42	0/42

Supportive studies

The supportive STOMP study Arm 2 has been described in section 4.4.1.

2.4.3. Discussion on clinical efficacy

The MAH is submitting a Grouped Type II /Type IB variation for selinexor (Nexpovio).

The **Type IB** variation relates to the introduction of a new pack size (8 tablets per pack) for added convenience to patients for dose modification in the new intended treatment setting.

The **Type II variation** is aimed at extending the indication for Nexpovio to be used:

"in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy".

In addition, results from the pivotal study in support of this application are intended to fulfil the Specific Obligation (SOB) in the context of the Conditional Marketing Authorisation (CMA) of Nexpovio (selinexor) which was granted on 26 March 2021.

This application is based on the efficacy results from the pivotal ongoing **phase 3 KCP-330-023 (BOSTON) study** and supported by the **Phase 1b/2 KCP-330-017 (STOMP) study**.

Dose finding – Dose response study

KCP-330-017 (STOMP) study is a multicenter, multi-arm, open-label, clinical study with a Dose-Escalation (Phase 1) and an Expansion (Phase 2) to independently assess the MTD/RP2D, safety, and efficacy in patients with either newly diagnosed MM or previously treated MM. The study includes 7 treatment arms.

Arm 2 of SVd (selinexor in combination with bortezomib and low-dose dexamethasone) was one of the combinations evaluated in STOMP study in patients with relapsed or refractory MM who had received at least one prior line of therapy. The primary endpoint of the phase 1 part was to establish MTD and define the RP2D dose. The primary endpoints of the Phase 2 include overall response rate (ORR), DOR, and clinical benefit rate (CBR).

Of the 42 patients treated on the SVd arm 40 patients were evaluable for efficacy. The ORR was 75% in patients with PI-nonrefractory MM (n = 20), while patients with PI-refractory MM (n= 20) had an ORR of 40%. As reported by the MAH, the PI-refractory population is a more pre-treated population (median of 6.5 previous lines, 85% of patients with more than 3 lines, with 100% of patients exposed to lenalidomide and 75% of refractory to lenalidomide and/or pomalidomide), and with different characteristics from those proposed in the BOSTON study. Therefore, the "BOSTON-like" population is the non-PI refractory population and results in this subset of patients guided next steps of the development.

The RP2D of SVd in the STOMP study was established to be selinexor 100 mg QW and bortezomib 1.3 mg/m2 QW plus dexamethasone 40 mg QW. Selinexor 100 mg QW showed a response rate similar to selinexor 80 mg BW with a lower cumulative dose and expected lower toxicity. The rationale for selecting this dose appears adequate also given the efficacy results reported in the "BOSTON-like" population (see above).

Of note, as concomitant therapy all patients must receive 5-HT3 antagonists (ondansetron or equivalent) during selinexor treatment. Additionally, it has been reported by the MAH that supportive measures for optimal medical care should be provided as appetite stimulants (megestrol acetate), centrally acting agents and NK1R antagonist, given the fact that the main side effects have been primarily related to anorexia with poor caloric and fluid intake, fatigue, and nausea. This point raises concerns about tolerability of the drug.

Main clinical study

Design and conduct

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

As noted above the dose/regimen of SVd was selected on the basis of results from the phase 2 study STOMP, i.e. the observed activity of the combination and safety and tolerability considerations. This regimen allows patients in the experimental arm to receive approximately 40% less bortezomib and approximately 25% less dexamethasone than patients in the Vd arm since Vd is given at different dose in the experimental and control arms of the BOSTON study. The design is considered acceptable, but it is indeed not a classical add-on study with the same backbone in both treatments' arms, therefore preventing blinding which is a drawback of the current design.

The Vd regimen is still an acceptable option for patients with RRMM, although other options (such as lenalidomide + dexamethasone or carfilzomib + lenalidomide + dexamethasone or elotuzumab +

lenalidomide + dexamethasone) were approved for patients who have received at least one prior line of therapy, as well as pomalidomide + dexamethasone for those who have received at least two prior therapies, when the BOSTON study was planned. Indeed, although the control arm in the BOSTON study is an accepted standard of care, the room for improvement of response of a patient previously exposed to bortezomib, alone or in combination in a previous first line, appears limited with the proposed combination and in fact Vd is usually considered as an option in later lines of treatment. In this context, the control arm in the BOSTON study can be considered, at present, as a suboptimal treatment option in the intended treatment setting. This having said it is acknowledged that the treatment landscape for MM patients is evolving quickly and demonstration of superiority vs. the proposed control arm should in principle suffice for regulatory approval.

A total of 402 patients were randomized in a 1:1 ratio to either SVd (n=195) or Vd (n=207). Three hundred ninety-nine subjects (SVd: 195, Vd: 204) received study treatment. At the time of the clinical cut-off date of 18 Feb 2020, 19% SVd subjects and 17.6% of Vd subjects were still on study treatment.

Randomization was stratified by prior PI therapy (yes or no), number of prior anti-MM regimens (1 versus >1), and disease severity at study entry (based on the revised International Staging System [R-ISS]; Stage III versus Stage I or II). The 1:1 randomisation ratio is agreed, and the proposed stratification factors are considered acceptable as they represent basal characteristics with well-known potential impact on clinical responses. Furthermore, taking into account that both SVd and Vd are expected to rely on conserved sensitivity to bortezomib, stratification based on prior exposure to PI is agreed. Region 2 guarantees representation of the target population in the EU.

Following confirmation of progressive disease (PD) by the Independent Review Committee (IRC), patients who received Vd were allowed to cross over to receive either SVd (i.e. the SVdX treatment arm) or selinexor and low-dose dexamethasone (i.e. the SdX treatment arm) for those patients who were intolerant to bortezomib. The possibility offered to patients in the Vd arm to crossover to SVd appears reasonable also considering that there are some (preliminary) clinical data suggesting that selinexor is able to restore sensitivity to bortezomib. This was in fact agreed at the time when SA was sought. The generation of potential valuable information on the activity of SVd in patients resistant to bortezomib has however to be weighed against the potential impact of the crossover on the assessment of long-term time-dependent endpoints, especially OS which is a secondary endpoint in the BOSTON study. As discussed also during the SA, precise estimates of long-term OS in the targeted early stage of MM (1-3 prior lines) are not required for approval but rather the absence of a detrimental effect. This is so in view of the long-expected survival after progression. In this regard the MAH has conducted several OS sentivity analyses to account for the crossover. Further, the number of patients who crossed over is limited, and therefore not expected to have a major impact on the results of the study. The proposed rules for prevention of premature cross over are overall supported.

The MAH states that 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. Upon request the MAH provided information that for the primary analysis, 3 patients (SVd n=2; Vd n=1) had only one progression as the last MM assessment and that at the time of the DCO date for the updated analysis, 5 patients (SVd n=3; Vd n= 2) had only 1 progression as the last MM assessment. The MAH confirmed that these eight patients were not counted as PFS events but censored.

The **target population** of the study is considered well represented. Overall, the proposed inclusion and exclusion criteria are supported. In the study patients were included based on investigator-based evidence of PD and had confirmed PD, i.e. they were required to have confirmed PD on or after their most recent regimen based on the Investigator's assessment (Inclusion Criterion #3).

Regarding patient demographics, the median ages of the patients in BOSTON were 66 and 67 years in the SVd and Vd arms, respectively. The majority of the patients were 65 years of age or older (SVd, 55.9%; Vd, 63.8%) and ~20% were ≥75 years of age. More males were enrolled in the study than females (males: SVd, 59.0%; Vd, 55.6%) and the race was predominantly white (SVd, 82.6%; Vd, 79.7%).

Patients with plasma cell leukemia, associated AL amyloidosis, CNS involvement or POEMS syndrome were excluded from trial participation to reduce heterogeneity. This has been reflected in the SmPC.

Approximately 50% of the patients had received 1 prior anti-MM therapy (SVd: 50.8%; Vd: 47.8%) with one-third having 2 prior regimens, and the remainder having 3 prior regimens for MM.

A slightly higher previous exposure to bortezomib-dexamethasone is reported in the Vd arm, although overall, bortezomib previous exposure was similar in both treatment arms. Bortezomib–refractoriness was numerically slightly higher in the Vd treatment arm, as well as Thalidomide refractoriness and IMiD refractoriness in general. Median previous treatment lines were 2 in the Vd arm, whereas in the SVd arm median previous lines of treatment was 1.The reported differences are generally small, and it is not considered that they can have a significant impact on the results.

Regarding refractoriness, bortezomib refractory patients were excluded. The following was required for patients previously treated with bortezomib (inclusion criteria):"Best response achieved with prior bortezomib at any time was ≥PR and with the last PI therapy (alone or in combination) was ≥PR AND participant did not discontinue bortezomib due to Grade ≥3-related toxicity AND must have had at least a 6-month PI-treatment-free interval prior to C1D1 of study treatment." All patients in the BOSTON study who had achieved a response to lines of prior therapy that included bortezomib had been treated with that therapy for at least 60 days and/or achieved a response to a bortezomib-containing therapy that lasted for >60 days, with except one patient. This patient was previously exposed to bortezomib and achieved less that PR. However, bortezomib exposure was too short to consider refractoriness. Additionally, this patient was treated in the Vd arm achieving a VGPR, what is understood as bortezomib sensitivity.

Several patients in the BOSTON study received stem cell transplantation (SCT). It is assumed that only autologous stem cell transplant (ASCT) has been considered, as patients are in earlier lines of therapy. However, the uncertainty surrounding the allogeneic SCT and the impact it may have on subsequent treatments should be taken into account. In the 8 patients in whom the type of transplant is unknown, it cannot be assumed, in the absence of indirect data that would suggest so, that it was an autologous transplant. The MAH has provided additional information on these 8 patients with "unspecified type of transplant", in terms of previous therapies and subsequent clinical outcomes. As per the reported data, an autologous STC transplant is the most likely procedure conducted in these patients. One out of these 8 patients achieved a PR after receiving selinexor in combination.

According to the current ESMO guideline, in MM for fit newly diagnosed MM (NDMM) patients, aged 70 years, without comorbidities, induction followed by high-dose therapy (HDT) with autologous stem cell transplantation (ASCT) and lenalidomide maintenance is the recommended treatment. In this context, it is surprising that only 39% of the included patients have received an ASCT before entering the study, given that this treatment option is considered as a standard of care in newly diagnosed MM (NDMM) patients in many countries. The MAH reported that 33% of patients were >70 years old at enrolment (at diagnosis 24% of patients were >70 years old) and would generally not be considered for ASCT per the ESMO guidelines. The proportion of patients who received a previous transplant was higher in the study arm (SVd) than in the control arm (Vd). No relevant differences in efficacy among the two groups, with and without prior SCT, were however reported.

In the SVd arm of the supportive study STOMP 7 out of 12 patients with PI-refractory MM responded (ORR 58%). These patients with PI-refractory MM are similar to the ones treated in the Vd Arm of the BOSTON study who will be given the opportunity to cross over to SVd. Since preliminary clinical data suggest that selinexor is able to restore sensitivity to bortezomib, this is acceptable and could provide additional valuable information on the activity of SVd in patients resistant to bortezomib.

As reported by the MAH, 63 patients from the Vd arm crossed-over to SVdX (regarding ITT population 111/207 Vd treated patients were reported as PD and 74 crossed-over: 11 crossed to SdX and 63 to SVdX). The ORR in these 63 patients under SVdX was 19% (3 patients (4.8%) achieved VGPR and 9 patients (14.3%) achieved a PR). Nine (14.3%) patients achieved a MR, 30 patients (47.6%) SD, 5 patients (7.9%) showed PD, and 7 patients (11.1%) were not evaluable. Median PFS in these 63 patients was 3.91 months (95% CI: 3.48 to 6.93). As of the database cut-off date (14 February 2021) the median (95% CI) duration of response in the SVdX population was 5.78 months (4.34, NE). Of the 11 patients in the SdX population, 1 (9.1%) patient achieved a very good partial response, 8 (72.7%) patients achieved stable disease, 1 (9.1%) patient had progressive disease (PD), and 1 patient's response was non-evaluable. Based on the IRC assessment, at the time of the data cut-off date, from these SdX treated patients 6 patients had events, 5 (45.5%) had PD and 1 (9.1%) patient died. The median (95% CI) PFS was 2.33 months (2.30, non-evaluable)

The main hypothesis of the BOSTON study is of superiority of SVd compared with Vd for the **primary efficacy endpoint** progression free survival (**PFS**), based on IRC assessment. Disease response has been assessed according to the International Myeloma Working Group (IMWG) response criteria for MM (Kumar 2016). The BOSTON study was originally designed with PFS and ORR as co-primary endpoints. At the time when scientific advice was sought, the MAH was however discouraged to include ORR as co-primary endpoint in the context of such an early stage of relapse (1-3 prior therapies, no refractoriness to bortezomib), when relatively high response rates are still expected, questioning the relative value of that endpoint. Further, the MAH was discouraged to use ORR results for a potential conditional approval, since ORR is not currently recognized as a reliable surrogate for PFS (or OS) in RRMM, and the actual value of endpoints based on response rates to define clinical benefit in the absence of long-term data is still debated. PFS was recommended as the primary endpoint, consistent with all recent approvals in MM. In this regard, the design was modified (Protocol Version 4.0 dated 17 August 2018) and PFS became the single primary endpoint. ORR was moved to a secondary endpoint.

Secondary objectives included to compare the 2 arms in terms of overall response rate (ORR) (≥partial response [PR]), as well as number of patients achieving ≥ very good partial response (VGPR), ≥ complete response (CR) or minimal residual disease (MRD) negative (for patients who achieve CR or stringent CR [sCR]. An additional secondary objective was to compare the incidence of any Grade ≥2 peripheral neuropathy events between the two arms (see safety section). Other secondary endpoints include overall survival (OS), duration of response (DOR) and time to next treatment (TTNT).

A number of (major) amendments were made to the **protocol** including changes in the primary endpoint(s), number of events required for the analyses (final and interim; see below), definition of response, etc. These revisions together with the late finalization of the SAP including a major change affecting the primary efficacy analysis in the context of open-label study called into question the integrity of the study. To address these concerns the MAH presented a detailed description on how the data integrity was maintained from the beginning of the trial until the data cut-off when the pre-planned second IA for efficacy was changed into the final analysis, at a very late stage. Apparently, the main reason to have performed this major change was due to predictions that the 267 PFS events planned would not be achieved in a reasonable period of time. In addition, the MAH presented relevant information on a calendar time basis from the beginning of the trial, including amendments in the protocol, SAP and interactions with the DSMB. The justification of the MAH was acknowleged and it appeared that they remained blinded to the results.

A GCP inspection was conducted as proposed by the CHMP, bearing in mind what was stated in the Integrated Inspection Report (IIR) of the routine GCP inspection requested by the CHMP at the time of initial MAA (GCP/2019/001); see section 4.1.4. The IIR from this new inspection was submitted on 17th March 2022. According to it, although certain measures had been implemented after the first inspection, which was performed at the time of the initial CMA application, critical findings in relation to the clinical conduct and management of the trial by the Sponsor were identified. Based on these several critical findings, the inspectors could not confirm that trial data were reliable and had adequate quality to be used in support of the applied extension of the indication for Nexpovio. Importantly, the inspectors identified "*a risk of potentially biased decisions been taken by potentially unblinded key personnel from the Cy and a risk of introducing bias on IRC members' assessment*". This is of special relevance since the primary endpoint in the BOSTON trial was PFS by the IRC. At the time of the primary analysis a statistically significant improvement in PFS was observed (see below). In addition, a sensitivity analysis, where the confirmation of PD was based on the investigator's assessment instead of the IRC's assessment, was conducted and showed consistent results, i.e. median PFS was 13.93 months (95% CI: 11.73, NE) in the SVd arm and 9.46 months (95% CI: 8.44, 11.89) in the Vd arm; HR 0.73 (95% CI: 0.55, 0.98). This is reassuring. However, the BOSTON study is an open label study and concerns affecting the assessment of the primary endpoint of PFS by IRC could be expected to have resulted in loss of control of type I error questioning the robustness of the results. In this context, OS data (which was a secondary endpoint in the trial) could be considered of special relevance. Reported OS results in the BOSTON study are included below, showing that a detrimental effect of SVd in terms of OS does not seem likely, though still these data corresponded to 148 survival events (37%, n=402) (DCO 15 Feb 2021). In the context of the reported GCP findings a further update of OS data was provided corresponding to 157 survival events (DCO 22 March 2022). Results seem overall consistent and supportive of benefit of selinexor in the claimed indication.

Further, based on the criticality of the GCP findings identified, the MAH was requested to address them (by conducting a reanalysis of data used by the IRC to determine progression of the disease) and justify how the provided data can be considered reliable to support a B/R assessment. The IRC data review consisted of two parts (Part 1 and Part 2). Part 1 was comprised of the assessment from each IRC member while Part 2 was an adjudication meeting between the IRC members, to achieve consensus, in which the Sponsor was also present (according to the MAH for administrative and training purposes only). To address the identified concerns, the MAH has provided (instead of a full reanalysis) a sensitivity analysis of PFS results using only data from Part 1 of the 'IRC data review' without any information from Part 2 (adjudication meeting). According to this sensitivity analysis (of PFS assessment review), only for 10 patients (3 in the SVd arm and 7 in the Vd arm) the PFS assessment was affected (~2.5% of all randomised patients in the study). Among those 10 patients in whom changes in the adjudication affected PFS, a total of 5 (2 in the SVd arm and 3 in the Vd arm) had their PFS event/censoring status affected, which is balanced between the two treatment arms. Median PFS (95% CI) according to this analysis is of 13.93 (11.73, NE) vs. 9.46 (8.11, 10.87) months for the SVd and Vd arms, respectively. These results are in line with data reported in the primary efficacy analysis in the BOSTON study (see below). The reported HR (95% CI) for this sensitivity analysis, i.e. 0.7058 (0.5303, 0.9395), is also consistent with that of the primary analysis. Taking all these into account and considering that PFS results according to the investigator are also consistent, the reported PFS data can be considered reliable to support B/R assessment.

Statistical aspects

There were 3 versions of the SAP (Version 1.0 dated 15 August 2018, Version 2.0 dated 30 September 2019, and Version 3.0 dated 24 February 2020).

Two interim analyses were planned with different objectives. The first (unblinded) interim analysis (IA) was conducted to assess the conditional power at the time when approximately 30% PFS events had been achieved to consider if a sample size re-estimation was necessary using the CHW method (Cui et al., 1999). This analysis was conducted with data cut of 21 Jan 2019 after 113 events were accrued. On 21 Feb 2019 the DSMB met and recommended continuing the study with no sample size adjustment and no change to the safety monitoring.

A second IA was planned after approximately 75% of PFS events had occurred that would have allowed for a conclusion of efficacy or to stop for futility. The MAH planned to use the Lan DeMets alpha spending function with the O'Brien-Fleming boundary. However, the MAH later decided to change the original design and to consider this second IA as the final efficacy analysis "no matter the outcome is positive or not". The MAH did not discuss their proposal with any regulatory Agency but instead notes that the DSMB agreed. Because of this decision the testing of the primary efficacy endpoint was done using all one-sided alpha of 0.025 instead of the corresponding level of alpha using the spending function originally proposed.

The decision to change the second IA into the final analysis using the full level of alpha was triggered at a very late stage. In fact, this change was included in an updated statistical analysis plan (Version 4.0) dated 24 Feb 2020 (see above), 6 days after the data cut-off for the primary efficacy endpoint (18 Feb 2020). To justify the change the MAH argues that there were concerns that the trial was not going to reach the planned 267 events, and that an extended period of time would have been needed to accrue additional PFS events with minimal gain in power. The provided justification was not entirely followed since a total of 204 PFS events were achieved at the time of submission (76.40% of planned events) and in the updated primary analysis one year later, a total of 229 of PFS events had been achieved (85.76% of planned events).

As stated above, considering the open-label design of the trial it was not possible to exclude that these changes were partially driven by data and therefore no formal adjustment for inference would be feasible translating into lack of type I error control. For that reason, and in order to assess the robustness of the results, the MAH was requested to submit the analyses for the primary efficacy endpoint considering the corresponding alpha value using the Lan DeMets alpha spending function with the O'Brien-Fleming boundary as initially proposed (pre-planned IA2). Using the alpha spending function as initially planned, the boundary p-value would have been 0.0103 instead of the 0.025 used for the primary efficacy analysis and still the results are statistically significant.

Efficacy data and additional analyses

All efficacy analyses were conducted using the **ITT population**; all tests (log-rank tests, Cochran-Mantel-Haenszel tests) were one-sided.

Updated data as of 15 Feb 2021 cut-off date (i.e. from an additional year of follow-up) were also submitted by the MAH and included updated results for the primary endpoint, key secondary endpoints, and safety data: cumulative PFS, DOR, OS, ORR, AEs, SAEs, AECIs, and deaths.

Primary endpoint

The BOSTON study met its **primary endpoint**. A statistically significant improvement in median PFS in the SVd arm (13.93 months) compared with the Vd arm (9.46 months; p=0.0075; HR, 0.70; 95% CI: 0.5279-0.9335) was reported at a median overall follow-up of 13.17 and 16.53 months for the SVd and Vd arms, respectively. The results were generally consistent across multiple sensitivity analyses (including according to EMA censoring rules) and across pre-specified subgroups by relevant patient and disease characteristics, including regardless of prior therapeutic regimens. Results from the updated analysis were also consistent. However, it is noted that the median follow-up for Vd in the updated analysis is 24.48 (21.16- 29.17) months, which is 11 months longer (almost double) than that reported

for the SVd arm of 13.47 (10.64-24.87) months, with a wider range. Of note, patients were not always followed after treatment discontinuation, but only when they "were willing to continue survival follow-up, still alive, not lost to follow-up and have not discontinued from the study". As reported by the MAH, the SVd arm had a higher proportion of patients censored in PFS analysis compared to the Vd arm, explaining why the estimated median follow-up time using the reverse KM method is shorter for SVd.

Secondary endpoints

Among the key secondary endpoints, a statistically significant improvement in **ORR** from 62.3% (95%CI: 55.3, 68.9) in the Vd arm to 76.4% (95%CI: 69.8, 82.2) in the SVd arm (p=0.0012) was reported. The rate of ≥VGPR improved from 32.4% in the Vd arm to 44.6% in the SVd arm. In terms of ORR, the results observed in the updated analysis were consistent with the previously reported in the primary analysis. It has been reported that 9 of 33 patients (27%) with sCR or CR from the SVd arm and 8 of 22 patients (36%) with sCR or CR from the Vd arm were assessed as MRD negative. These data suggest that no deeper responses are achieved in patients treated with selinexor, with MRD negativity percentages lower in the SVd arm.

The median **DOR** according to the primary analysis were 20.3 (95% CI: 12.55, NE) months in the SVd arm and 12.9 (95% CI: 9.26, 15.77) months in the Vd arm. In the updated analysis, median DOR has been reported as 17.3 months (95% CI: 12.55, 26.25) in the SVd arm and 12.9 months (95% CI: 9.26, 15.77) in the Vd arm. The MAH was requested to submit a further update of the DoR results and it was confirmed that the median DOR remained the same as of 01 December 2021.

A clinically significant increase in the **TTNT** was achieved with the proposed SVd regimen. The median TTNT in the SVd arm was 16.1 months (95% CI: 13.9, NE) compared to 10.8 months (95% CI: 9.8, 13.4) in the Vd arm.

Median OS was not reached for SVd at a median follow-up of 17.3 months (primary analysis). The median OS for patients in the Vd arm was 24.97 months (95% CI: 23.49, NE). In the updated efficacy analysis at a median follow-up of 28.71 months, the median OS was 36.67 months (95% CI: 30.19, NE) for SVd compared to 32.76 months (95% CI: 27.83, NE) in the Vd arm; HR=0.88 (95% CI: 0.63, 1.22). At that time, data were immature but a detrimental effect of SVd in terms of OS did not seem likely also bearing in mind that cross-over was allowed in the BOSTON study. As already stated, further OS data were provided during the procedure with a median follow-up of 33.6 months in the SVd arm and 33.84 months in the Vd arm, which remained overall consistent with the previous data submitted (HR 0.93; 95% CI: 0.67, 1.27).

Additional expert consultation

N/A

Assessment of paediatric data on clinical efficacy

N/A

2.4.4. Conclusions on the clinical efficacy

Treatment with the (once weekly) combination of selinexor with bortezomib and dexamethasone tested in the BOSTON study (SVd) leads to a significant improvement in median PFS compared to the standard (BIW) Vd regimen in the targeted patient population, i.e. adult patients with MM who have received at least one prior therapy. This benefit in terms of PFS is supported by several secondary endpoints. Importantly, no evidence of detrimental effect on survival has been observed also considering that cross over, to either SVd or Sd, was allowed in the trial.

2.5. Clinical safety

Introduction

The primary study supporting this Type II Variation is the Phase 3 confirmatory **Study KCP-330-023 (BOSTON)**, in which adult patients with MM who had received 1 to 3 prior MM regimens were randomized 1:1 to receive QW SVd versus BIW Vd. Of note, in the SVd arm, selinexor and bortezomib are administered QW, whereas in the Vd arm, bortezomib is administered BIW (consistent with the bortezomib label) with both regimens given with low-dose dexamethasone. At the time of primary analysis (18 Feb 2020), BOSTON was ongoing and had completed enrolment with 402 patients (195 randomized to SVd and 207 to Vd) of whom 203 remained on study (102 and 101 in the SVd and Vd arms, respectively). Updated analysis for BOSTON study data included in this Type II Variation submission has a data cut-off date of 15 Feb 2021.

In addition to this primary study, supporting safety data are provided from the preceding Phase 1b/2 **study (KCP-330-017) STOMP**. The enrolment in the SVd arm (Arm 2) of STOMP was completed as of 01 Sep 2019, with 42 patients dosed, of whom 2 remained on study.

Table 1: Company-Sponsored Pivotal and Supportive Studies for Type II Variation

	Pivotal Study	Supportive Study
	KCP-330-023 (BOSTON)	KCP-330-017 (STOMP)
Number of patients	258[a]	42
Population	Relapsed or refractory multiple myeloma	Relapsed/refractory multiple myeloma
Study status	Ongoing	Ongoing[b]
Prior therapies	Patients who had at least 1 prior anti-MM regimen and no more than 3 prior anti-MM regimens. Induction therapy followed by stem cell transplant and consolidation/maintenance therapy was considered as 1 anti-MM regimen	Arm 2 (SVd) in RRMM: Patients whose MM was relapsing after ≥1 line of therapy, and whose MM was not refractory to bortezomib in their most recent line of therapy (i.e., relapsed but not refractory to prior bortezomib therapy). Note: 19 of the 42 patients from the SVd arm of STOMP would have been eligible for BOSTON. The remaining patients were more heavily pretreated and/or had disease refractory to proteasome inhibitors
Dose	Selinexor: 100 mg PO on Days 1, 8, 15, 22, and 29 of each 35-day cycle Bortezomib: 1.3 mg/m² SC on Days 1, 8, 15, and 22 of each 35-day cycle Dexamethasone: 20 mg PO on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle **Vd arm:** **First 8 cycles:** Bortezomib: 1.3 mg/m² SC on Days 1, 4, 8, and 11 of each 21-day cycle. Dexamethasone: 20 mg PO dose on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle. **Cycles ≥9** Bortezomib 1.3 mg/m² SC on Days 1, 8, 15, and 22 of each 35-day cycle. Dexamethasone: 20 mg PO dose on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle. **SVdX arm:** Patients who crossed over from Vd treatment to SVdX following the Cycle 1 of SVd treatment as described above.	**Dose escalation:** **Bortezomib QW schedule: (35 days cycle), 7 patients:** Selinexor: 80/100 mg PO QW on Days 1, 8, 15, 22, and 29 of each 35-day cycle Bortezomib: 1.3 mg/m² SC QW on Days 1, 8, 15, and 22 of each 35-day cycle Dexamethasone: 40 mg PO QW Days 1, 8, 15, 22, and 29 of each 35-day cycle **Bortezomib BIW schedule: (21 days cycle), 6 patients:** Selinexor: 80 mg PO QW on Days 1, 8, and 15 of each 21-day cycle Bortezomib: 1.3 mg/m² SC QW on Days 1, 4, 8, and 11 of each 21-day cycle Dexamethasone: 40 mg PO QW Days 1, 8, and 15 of each 21-day cycle **Selinexor BIW schedule: (35-day cycle), 9 patients:** Selinexor: 60/80 mg PO BIW on Days 1, 3, 8, 10, 15, 17, 22, and 24 of each 35-day cycle Bortezomib: 1.3 mg/m² SC QW on Days 1, 8, 15, and 22 of each 35-day cycle Dexamethasone: 20 mg PO BIW on Days 1, 3, 8, 10, 15, 17, 22, 24, 29, and 31 of each 35-day cycle
		Dose Expansion, 20 patients: As of Protocol, v.3.0, the RP2D for SVd in the expansion phase was determined to be selinexor 100 mg + dexamethasone 40 mg + bortezomib 1.3 mg/m² SC, all QW. If a patient did not have at least a PR after 2 cycles at the RP2D (and have no AEs >Grade 2 [CTCAE 4.03] at the time of dose escalation), the Sd dose was escalated to selinexor 60 mg + dexamethasone 20 mg, BIW (total weekly selinexor dose = 120 mg).

Source: Module 5.3.5.2, Study KCP-330-017 CSR, Protocol version 5.0 and Module 5.3.5.1, Study KCP-330-023 CSR, Protocol version 4.0.
AE: adverse event; BIW: twice weekly; CTCAE: Common Terminology Criteria for Adverse Events; MM: multiple myeloma; PO: orally; PR: partial response; QW: once weekly; RP2D: recommended Phase 2 dose; RRMM: relapsed or refractory multiple myeloma; SC: subcutaneously; SVd: selinexor with bortezomib and dexamethasone; SVdX: patients who crossed over from Vd to SVd treatment; Vd: bortezomib and dexamethasone.
[a] including the primary safety population and the SVdX patients.
[b] Enrollment has been completed for SVd arm in KCP-330-017 (STOMP).

The SCS includes an integrated summary of the safety from these 2 company-sponsored clinical studies evaluating selinexor in patients with MM.

Table 2: Pivotal and Supportive Studies Contributing to Analysis Populations

Study	All SVd (N=300)	BOSTON SVd (N=195)	BOSTON Vd (N=204)
KCP-330-023	All patients dosed in SVd arm (195 [BOSTON] + 42 [STOMP] + 63 [SVdX population])	All patients dosed in SVd arm	All patients dosed in Vd arm
KCP-330-017	All patients dosed in SVd arm	–	–

d: dexamethasone; S: selinexor; V: bortezomib; X: crossover population.

Patient exposure

Table 3: Disposition of all Patients by Treatment Group, Safety Population – Updated Analysis

Disposition Category	All SVd (N=301[a]) n (%)	BOSTON SVd Arm (N=195) n (%)	BOSTON Vd Arm (N=204) n (%)
Enrolled patients in treatment group	301 (100.0)	195 (100.0)	204 (100.0)
End-of-treatment disposition			
On-treatment	24 (8.0)	21 (10.8)	16 (7.8)
Discontinued treatment and reasons	277 (92.0)	174 (89.2)	188 (92.2)
Disease progression	128 (42.5)	76 (39.0)	118 (57.8)
Withdrawal by patient	54 (17.9)	37 (19.0)	21 (10.3)
Adverse event/toxicity to study drug	52 (17.3)	33 (16.9)	26 (12.7)
Death	24 (8.0)	14 (7.2)	14 (6.9)
Lost to follow-up	3 (1.0)	3 (1.5)	2 (1.0)
Non-compliance with study drug/protocol deviation	4 (1.3)	1 (0.5)	2 (1.0)
Physician decision	11 (3.7)	10 (5.1)	5 (2.5)
Other	1 (0.3)	0	0
Patients in survival follow-up[b]	72 (23.9)	52 (26.7)	58 (28.4)
Patients who have completed survival follow-up	18 (6.0)	0	0
Patients who die during survival follow-up	97 (32.2)	54 (27.7)	55 (27.0)
Patients who discontinued from the study without completing survival follow-up	16 (5.3)	13 (6.7)	16 (7.8)
End-of-study disposition			
On-study	96 (31.9)	73 (37.4)	78 (38.2)
Completed	18 (6.0)	0	0
Discontinued from study and reasons	187 (62.1)	122 (62.6)	126 (61.8)
Disease progression	1 (0.3)	0	0
Withdrawal by patient	49 (16.3)	39 (20.0)	39 (19.1)
Adverse event/toxicity to study drug	0	0	0
Death	121 (40.2)	68 (34.9)	79 (38.7)
Lost to follow-up	12 (4.0)	12 (6.2)	7 (3.4)
Non-compliance with study drug	0	0	0
Physician decision	2 (0.7)	1 (0.5)	0
Other	2 (0.7)	2 (1.0)	1 (0.5)

Data cut-off date: 15 Feb 2021 (BOSTON); 01 Sep 2019 (STOMP)
SVd: selinexor with bortezomib and dexamethasone; Vd: bortezomib and dexamethasone.
[a] All SVd population includes 195 patients from the BOSTON SVd arm + 64 patients from the BOSTON crossover arm (SVdX), including 1 additional patient who crossed over from the Vd arm since the primary analysis + 42 patients from the supportive study, STOMP.
[b] Patients in follow-up consists of patients who are willing to continue into survival follow-up, still alive, not lost to follow-up and have not discontinued from the study.

Table 4 below provides a summary of the exposure to study treatment by treatment group for all patients in the safety population based on updated analysis. One additional patient, who crossed over from Vd arm to the SVdX arm in BOSTON study since primary analysis (N=300), was included in the All SVd population for the updated analysis (N=301).

In the **All SVd population**, the median duration of exposure to SVd was 27.0 weeks (range: 1 to 206), with a majority (56.1%) of patients receiving study treatment for ≥24 weeks, and 29.2% of patients receiving treatment for ≥48 weeks.

In the **BOSTON SVd arm**, the median duration of exposure to study treatment was longer (30.0 weeks; range: 1 to 171), the proportion of patients treated for ≥48 weeks was higher (35.9% of patients), patients received a higher median number of doses (26.0), and a higher median total dose (2300.0 mg) of selinexor, than in the All SVd population. The longest duration of study treatment exposure was 171 weeks.

In the **BOSTON Vd arm**, the median duration of exposure to Vd was 32.0 weeks (range: 1 to 173), with a majority (60.3%) of patients receiving study treatment for ≥24 weeks, and 32.4% of patients receiving treatment for ≥48 weeks. The longest duration of study treatment exposure was 173 weeks.

Table 4: Exposure by treatment group - All Patients in the Safety Population

Parameter	All SVd (N = 301)	BOSTON SVd Arm (N = 195)	BOSTON Vd Arm (N = 204)
Duration of Selinexor Exposure (Weeks)			
n	301	195	0
Median	26.0	29.0	
Mean (STD)	40.9 (40.92)	47.2 (44.00)	
Min, Max	1 , 205	1 , 170	
Duration of Selinexor Exposure (Weeks), n (%)			
<2	6 (2.0)	2 (1.0)	0
2 - <4	10 (3.3)	4 (2.1)	0
4 - <12	46 (15.3)	25 (12.8)	0
12 - <24	71 (23.6)	44 (22.6)	0
24 - <48	83 (27.6)	53 (27.2)	0
>=48	85 (28.2)	67 (34.4)	0
Total Selinexor Dose Received (mg)			
n	301	195	0
Median	2000.0	2300.0	
Mean (STD)	3087.9 (2989.10)	3559.4 (3328.84)	
Min, Max	100 , 16800	100 , 16800	

Parameter	All SVd (N = 301)	BOSTON SVd Arm (N = 195)	BOSTON Vd Arm (N = 204)
Average Selinexor Dose Received per Week (mg/week) [1]			
n	301	195	0
Median	81.89	80.00	
Mean (STD)	80.41 (19.147)	78.89 (18.822)	
Min, Max	28.6 , 150.0	29.7 , 136.7	
Number of Selinexor Doses Received			
n	301	195	0
Median	24.0	26.0	
Mean (STD)	37.7 (38.14)	42.9 (41.55)	
Min, Max	1 , 168	1 , 168	
Patients with Dose Reduction to Selinexor, n (%)	177 (58.8)	128 (65.6)	0
Patients with Dose Delay/Interruption to Selinexor, n (%)	250 (83.1)	169 (86.7)	0
Patients with Dose Modification to Selinexor, n (%)	259 (86.0)	174 (89.2)	0
Patients with Missed Dose to Selinexor, n (%)	69 (22.9)	31 (15.9)	0
Patients with Dose Escalation to Selinexor, n (%)	71 (23.6)	48 (24.6)	0

Parameter	All SVd (N = 301)	BOSTON SVd Arm (N = 195)	BOSTON Vd Arm (N = 204)
Duration of Bortezomib Exposure (Weeks)			
n	301	195	204
Median	25.0	29.0	31.0
Mean (STD)	39.3 (39.87)	45.4 (42.73)	43.4 (39.18)
Min, Max	1 , 204	1 , 170	1 , 173
Duration of Bortezomib Exposure (Weeks), n (%)			
<2	7 (2.3)	2 (1.0)	2 (1.0)
2 - <4	8 (2.7)	4 (2.1)	8 (3.9)
4 - <12	48 (15.9)	25 (12.8)	30 (14.7)
12 - <24	75 (24.9)	47 (24.1)	44 (21.6)
24 - <48	84 (27.9)	55 (28.2)	55 (27.0)
>=48	79 (26.2)	62 (31.8)	65 (31.9)
Total Bortezomib Dose Received (mg)			
n	301	195	204
Median	40.8	46.1	72.6
Mean (STD)	63.2 (63.81)	72.0 (68.47)	90.3 (69.08)
Min, Max	2 , 335	3 , 335	2 , 327
Average Bortezomib Dose Received per Week (mg/week) [1]			
n	301	195	204
Median	1.71	1.70	2.46
Mean (STD)	1.72 (0.467)	1.70 (0.478)	2.49 (0.782)
Min, Max	0.6 , 5.2	0.6 , 5.2	0.9 , 5.7
Total Bortezomib Dose (mg/m^2) Received			
n	301	195	204
Median	22.25	25.36	40.28
Mean (STD)	33.64 (32.703)	38.45 (35.319)	49.38 (37.674)
Min, Max	1.3 , 176.1	1.3 , 176.1	1.3 , 197.5
Average Bortezomib Dose Received per Week (mg/m^2 per week) [1]			
n	301	195	204
Median	0.95	0.93	1.32
Mean (STD)	0.93 (0.219)	0.92 (0.225)	1.37 (0.402)
Min, Max	0.3 , 2.6	0.3 , 2.6	0.5 , 2.6

Parameter	All SVd (N = 301)	BOSTON SVd Arm (N = 195)	BOSTON Vd Arm (N = 204)
Number of Bortezomib Doses Received			
n	301	195	204
Median	19.0	21.0	31.5
Mean (STD)	28.1 (27.37)	32.4 (30.14)	39.7 (30.33)
Min, Max	1 , 135	1 , 135	1 , 151
Patients with Dose Reduction to Bortezomib, n (%)	111 (36.9)	85 (43.6)	93 (45.6)
Patients with Dose Delay/Interruption to Bortezomib, n (%)	241 (80.1)	160 (82.1)	151 (74.0)
Patients with Dose Modification to Bortezomib, n (%)	248 (82.4)	164 (84.1)	164 (80.4)
Patients with Missed Dose to Bortezomib, n (%)	68 (22.6)	34 (17.4)	38 (18.6)
Patients with Dose Escalation to Bortezomib, n (%)	10 (3.3)	10 (5.1)	7 (3.4)

Parameter	All SVd (N = 301)	BOSTON SVd Arm (N = 195)	BOSTON Vd Arm (N = 204)
Duration of Dexamethasone Exposure (Weeks)			
n	299	195	204
Median	26.0	30.0	31.0
Mean (STD)	41.0 (40.99)	47.5 (43.84)	43.2 (38.62)
Min, Max	1 , 206	1 , 171	1 , 173
Duration of Dexamethasone Exposure (Weeks), n (%)			
<2	4 (1.3)	1 (0.5)	2 (1.0)
2 - <4	11 (3.7)	5 (2.6)	8 (3.9)
4 - <12	48 (15.9)	26 (13.3)	30 (14.7)
12 - <24	71 (23.6)	42 (21.5)	42 (20.6)
24 - <48	78 (25.9)	51 (26.2)	58 (28.4)
>=48	87 (28.9)	70 (35.9)	64 (31.4)
Total Dexamethasone Dose Received (mg)			
n	299	195	204
Median	920.0	1080.0	1220.0
Mean (STD)	1314.0 (1283.87)	1520.4 (1375.80)	1616.7 (1341.30)
Min, Max	20 , 7200	40 , 6720	20 , 7200

Parameter	All SVd (N = 301)	BOSTON SVd Arm (N = 195)	BOSTON Vd Arm (N = 204)
Average Dexamethasone Dose Received per Week (mg/week) [1]			
n	299	195	204
Median	36.23	36.19	43.64
Mean (STD)	33.40 (7.219)	33.59 (6.958)	43.37 (13.099)
Min, Max	9.6 , 42.1	11.9 , 41.7	8.4 , 80.0
Number of Dexamethasone Doses Received			
n	299	195	204
Median	44.0	55.0	70.0
Mean (STD)	69.5 (70.55)	84.3 (78.13)	87.4 (71.26)
Min, Max	1 , 336	2 , 336	1 , 360
Patients with Dose Reduction to Dexamethasone, n (%)	72 (23.9)	55 (28.2)	74 (36.3)
Patients with Dose Delay/Interruption to Dexamethasone, n (%)	235 (78.1)	156 (80.0)	148 (72.5)
Patients with Dose Modification to Dexamethasone, n (%)	239 (79.4)	158 (81.0)	155 (76.0)
Patients with Missed Dose to Dexamethasone, n (%)	75 (24.9)	39 (20.0)	44 (21.6)
Patients with Dose Escalation to Dexamethasone, n (%)	8 (2.7)	7 (3.6)	10 (4.9)

(Database Cutoff Date: 2021-02-15; Source Data: ADBASE, ADEXSUM) Executed: 2021-03-09 11:08
Note: Study treatment is selinexor with bortezomib and dexamethasone for SVd treatment. Study treatment is bortezomib with dexamethasone for Vd treatment.
Note: Dose modification includes dose reduction, dose delay and dose interruption.
[1] Average dose received per week is defined as total dose received divided by duration of exposure.
F:\Biostatistics\KPT-330\ISS_BOSTON\Data_Cuts\2021-02-15\Dev\MAA_Update\T-14-1-8-1-Exposure-by-Treatment-Group-Safety-updated.sas

Adverse events

Table 5: Summary of Adverse Events By Treatment Group - All Patients in the Safety Population – Updated analysis

Patients with at Least One	All SVd (N = 301) n (%)	BOSTON SVd Arm (N = 195) n (%)	BOSTON Vd Arm (N = 204) n (%)
Treatment-Emergent Adverse Event	299 (99.3)	194 (99.5)	198 (97.1)
Grade 3/4 TEAE [1]	226 (75.1)	153 (78.5)	115 (56.4)
Grade 4 TEAE [1]	64 (21.3)	37 (19.0)	22 (10.8)
Serious TEAE	148 (49.2)	106 (54.4)	79 (38.7)
TEAE Leading to Dose Modification in Any Study Treatment [2] [3]	255 (84.7)	173 (88.7)	156 (76.5)
TEAE Leading to Dose Reduction in Any Study Treatment	194 (64.5)	141 (72.3)	106 (52.0)
TEAE Leading to Dose Interruption in Any Study Treatment	245 (81.4)	167 (85.6)	139 (68.1)
TEAE Leading to Study Treatment Discontinuation	67 (22.3)	41 (21.0)	34 (16.7)
TEAE Leading to Death	25 (8.3)	14 (7.2)	13 (6.4)
Treatment-Emergent Treatment-Related Adverse Event [4]	284 (94.4)	187 (95.9)	167 (81.9)
Grade 3/4 TRAE [1]	205 (68.1)	137 (70.3)	84 (41.2)
Grade 4 TRAE [1]	54 (17.9)	28 (14.4)	17 (8.3)
Serious TRAE	84 (27.9)	58 (29.7)	24 (11.8)
TRAE Leading to Dose Modification in Any Study Treatment [2] [3]	229 (76.1)	158 (81.0)	131 (64.2)
TRAE Leading to Dose Reduction in Any Study Treatment	190 (63.1)	139 (71.3)	102 (50.0)
TRAE Leading to Dose Interruption in Any Study Treatment	208 (69.1)	145 (74.4)	97 (47.5)
TRAE Leading to Study Treatment Discontinuation	53 (17.6)	32 (16.4)	27 (13.2)
TRAE Leading to Death	7 (2.3)	4 (2.1)	1 (0.5)

(Database Cutoff Date: 2021-02-15; Source Data: ADAE, ADDENOM) Executed: 2021-03-09 11:09
[1] Based on maximum severity grade of each patient.
[2] The number of patients with dose modification(s) is not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.
[3] Study treatment is selinexor with bortezomib and dexamethasone for SVd Arm, and bortezomib with dexamethasone for Vd Arm.
[4] An AE is considered treatment-related if it is selinexor-related and/or bortezomib-related and/or dexamethasone-related.

Common adverse events

Table 6: Treatment-Emergent Adverse Events occurring in ≥10% of Patients in the All SVd Population, Safety Population – Updated analysis

MedDRA Preferred Term	SVd Arm (N = 195) n (%)	Vd Arm (N = 204) n (%)	Total (N = 399) n (%)
Thrombocytopenia	121 (62.1)	56 (27.5)	177 (44.4)
Neuropathy peripheral	65 (33.3)	99 (48.5)	164 (41.1)
Anaemia	73 (37.4)	48 (23.5)	121 (30.3)
Fatigue	82 (42.1)	37 (18.1)	119 (29.8)
Nausea	98 (50.3)	21 (10.3)	119 (29.8)
Diarrhoea	65 (33.3)	52 (25.5)	117 (29.3)
Decreased appetite	69 (35.4)	11 (5.4)	80 (20.1)
Asthenia	49 (25.1)	27 (13.2)	76 (19.0)
Weight decreased	51 (26.2)	25 (12.3)	76 (19.0)
Upper respiratory tract infection	40 (20.5)	30 (14.7)	70 (17.5)
Constipation	33 (16.9)	36 (17.6)	69 (17.3)
Cough	36 (18.5)	31 (15.2)	67 (16.8)
Insomnia	31 (15.9)	32 (15.7)	63 (15.8)
Cataract	46 (23.6)	15 (7.4)	61 (15.3)
Back pain	31 (15.9)	29 (14.2)	60 (15.0)
Pneumonia	29 (14.9)	29 (14.2)	58 (14.5)
Pyrexia	31 (15.9)	26 (12.7)	57 (14.3)
Oedema peripheral	23 (11.8)	29 (14.2)	52 (13.0)
Vomiting	40 (20.5)	10 (4.9)	50 (12.5)
Bronchitis	25 (12.8)	21 (10.3)	46 (11.5)
Dyspnoea	18 (9.2)	28 (13.7)	46 (11.5)
Neutropenia	30 (15.4)	13 (6.4)	43 (10.8)
Dizziness	24 (12.3)	9 (4.4)	33 (8.3)
Headache	20 (10.3)	13 (6.4)	33 (8.3)
Nasopharyngitis	23 (11.8)	10 (4.9)	33 (8.3)

In the updated analysis, the **most frequently reported TEAEs** in the All SVd population and BOSTON SVd arm, all of which occurred at a higher frequency compared with the BOSTON Vd arm, were thrombocytopenia (58.5% and 62.1%, respectively), compared with 27.5% in BOSTON Vd arm; nausea (49.8% and 50.3%), compared with 10.3% in BOSTON Vd arm; fatigue (40.9% and 42.1%), compared with 18.1% in BOSTON Vd arm; anaemia (39.9% and 37.4%), compared with 23.5% in BOSTON Vd arm; decreased appetite (37.2% and 35.4%), compared with 5.4% in BOSTON Vd arm; and diarrhoea (34.6% and 33.3%) compared with 25.5% in BOSTON Vd arm.

Peripheral neuropathy was the most frequently reported TEAE (48.5%) in the BOSTON Vd arm compared with the All SVd population (28.2%) and BOSTON SVd arm (33.3%).

The incidence of **Grade ≥3 TEAEs** as of the updated analysis data cut was higher in the All SVd population (83.4%) and the BOSTON SVd arm (85.6%) compared with the BOSTON Vd arm (62.7%).

The most frequent (≥10.0%) Grade 3/4 TEAEs in the All SVd population compared with the BOSTON Vd arm were thrombocytopenia (39.9% and 17.6%, respectively), anaemia (20.3% and 9.8%, respectively), fatigue (11.3% and 1.0%, respectively), neutropenia (12.6% and 3.4%, respectively), and cataract (10.0% and 2.0%, respectively). Grade 3/4 TEAEs of PN were reported at a higher frequency in the BOSTON Vd arm compared with the All SVd population (8.8% and 3.7%, respectively).

Treatment-Emergent Grade 3/4 Adverse Events Occurring in ≥5% of Patients in Either Group (Safety Population)

MedDRA Preferred Term	All SVd (N = 301) n (%)	SVd Arm (N=195) n (%)	Vd Arm (N=204) n (%)
Patients with At Least One Treatment-Emergent Grade 3/4 Adverse Event	226 (75.1)	153 (78.5)	115 (56.4)
Thrombocytopenia	120 (39.9)	79 (40.5)	36 (17.6)
Pneumonia[a]	31 (10.3)	24 (12.3)	21 (10.3)
Anaemia	61 (20.3)	32 (16.4)	20 (9.8)
Fatigue	34 (11.3)	26 (13.3)	2 (1.0)
Peripheral neuropathy	11 (3.7)	9 (4.6)	18 (8.8)
Asthenia	18 (6.0)	16 (8.2)	9 (4.4)
Neutropenia	38 (12.6)	18 (9.2)	7 (3.4)
Cataract	30 (10.0)	22 (11.3)	4 (2.0)
Nausea	20 (6.6)	15 (7.7)	0
Diarrhoea	17 (5.6)	13 (6.7)	1 (0.5)
Hypophosphatasemia	15 (5.0)	11 (5.6)	3 (1.5)
Hyponatremia	16 (5.3)	9 (4.6)	1 (0.5)

Source: Table 14.3.1.2.1.4, Table 14.3.2.1.1.7

[a] Adverse events of pneumonia grouped by CMQ.

Treatment-related adverse events

Table 7: Treatment-related adverse events occurring in ≥5% of Patients in the All SVd Population, Safety Population – Updated analysis

MedDRA Preferred Term	SVd Arm (N = 195) n (%)	Vd Arm (N = 204) n (%)	Total (N = 399) n (%)
Thrombocytopenia	112 (57.4)	48 (23.5)	160 (40.1)
Neuropathy peripheral	63 (32.3)	96 (47.1)	159 (39.8)
Nausea	93 (47.7)	12 (5.9)	105 (26.3)
Fatigue	69 (35.4)	19 (9.3)	88 (22.1)
Decreased appetite	63 (32.3)	8 (3.9)	71 (17.8)
Diarrhoea	38 (19.5)	31 (15.2)	69 (17.3)
Anaemia	44 (22.6)	18 (8.8)	62 (15.5)
Insomnia	29 (14.9)	27 (13.2)	56 (14.0)
Asthenia	38 (19.5)	11 (5.4)	49 (12.3)
Weight decreased	38 (19.5)	8 (3.9)	46 (11.5)
Constipation	18 (9.2)	25 (12.3)	43 (10.8)
Cataract	35 (17.9)	6 (2.9)	41 (10.3)
Vomiting	34 (17.4)	5 (2.5)	39 (9.8)
Neutropenia	27 (13.8)	7 (3.4)	34 (8.5)
Oedema peripheral	15 (7.7)	17 (8.3)	32 (8.0)
Dyspnoea	11 (5.6)	13 (6.4)	24 (6.0)
Pneumonia	10 (5.1)	10 (4.9)	20 (5.0)
Vision blurred	10 (5.1)	8 (3.9)	18 (4.5)
Paraesthesia	4 (2.1)	12 (5.9)	16 (4.0)
Hyponatraemia	13 (6.7)	2 (1.0)	15 (3.8)
Pyrexia	12 (6.2)	3 (1.5)	15 (3.8)
Dizziness	11 (5.6)	3 (1.5)	14 (3.5)
Visual impairment	12 (6.2)	2 (1.0)	14 (3.5)
Dysgeusia	12 (6.2)	1 (0.5)	13 (3.3)
Alanine aminotransferase increased	10 (5.1)	1 (0.5)	11 (2.8)
Confusional state	11 (5.6)	0	11 (2.8)

The overall incidence of TRAEs as of the updated analysis data cut was higher in the All SVd population and BOSTON SVd arm compared with the BOSTON Vd arm (94.4% and 95.9%, respectively vs 81.9%) and the imbalance was primarily due to the known AEs of selinexor.

The most common TRAEs (reported in ≥20% patients in the All SVd population), which were reported more frequently in the All SVd population and BOSTON SVd arm than the BOSTON Vd arm, were thrombocytopenia (53.5% and 57.4%, respectively, vs 23.5%), nausea (47.2% and 47.7%, respectively, vs 5.9%) fatigue (34.2% and 35.4%, respectively vs 9.3%), decreased appetite (34.2% and 32.3%, respectively, vs. 3.9%), diarrhoea (23.3% and 19.5%, respectively vs. 15.2%), anaemia (22.3% and 22.6%, respectively, vs. 8.8%), and weight decreased (21.6% and 19.5%, respectively, vs. 3.9%).

Treatment-related PN was more frequently reported in the BOSTON Vd arm (47.1%) than the All SVd population (26.9%) and BOSTON SVd arm (32.3%).

Incidence of any Grade ≥2 peripheral neuropathy events (secondary endpoint)

As of the updated analysis data cut-off date (15 Feb 2021), Grade ≥2 PN events were reported in a total of 42 (21.5%) patients in the SVd arm and 73 (35.8%) patients in the Vd arm.

Incidence of Grade ≥2 Peripheral Neuropathy Events by Treatment Arm (Safety Population) – Updated Analysis

	SVd Arm (N=195)	Vd Arm (N=204)
Patients with At Least 1 Grade ≥2 Peripheral Neuropathy Events, n (%)	42 (21.5)	73 (35.8)
Grade 2	33 (16.9)	55 (27.0)
Grade 3	8 (4.1)	18 (8.8)
Grade 4	1 (0.5)	0
Grade 5	0	0
Cochran-Mantel-Haenszel Test (SVd vs Vd)[a]		
Odds Ratio (95% CI)	0.4878 (0.3124, 0.7617)	
One-sided P-value	0.0008	
Breslow-Day Test for Homogeneity		
P-value	0.6722	

Source: Table 14.3.3.1.1_updated.
Data cutoff date: 15 Feb 2021
For patients who cross over, peripheral neuropathy events that occurred after the crossover are not included.
Severity grade presented is the maximum grade of each patient.

Serious adverse event/deaths/other significant events

Deaths

In the **All SVd population**, 31 (10.3%) patients died within 30 days of last dose of study treatment. Of the 31 patients, 24 (7.9%) had the primary cause of death attributed to AEs and 7 (2.3%) patients died due to PD.

In the **BOSTON study**, as of the updated analysis data cut, a total of 148 (36.8%) patients died on the study (before withdrawal of consent): 68 (16.9%) patients in the SVd arm and 80 (19.9%) patients randomized in the Vd arm. Of the 80 deaths that occurred in the Vd arm, one of the deaths occurred in a patient prior to initiation of therapy and is therefore not included in the Safety Population. A total of 34 (8.5%) patients in the safety population died on treatment or within 30 days of last dose of study drug, with a similar frequency in the 2 treatment arms (8.2% and 8.8% in SVd and Vd arms, respectively). Among the 148 patients who died on study, the most common cause of death was PD in both the SVd arm (33/68 [48.5%]) and Vd arm (35/80 [43.8%]). Patients with TEAEs leading to death were comparable between the 2 arms with 14 (7.2%) patients in the SVd arm and 13 (6.4%) patients in the Vd arm.

Four of the 13 deaths due to TEAEs on the SVd arm occurred in India during the period between 2 Aug 2018 and 31 Oct 2018; no deaths on the Vd arm occurred in India. Thus, one-third of the TEAEs leading to death on SVd occurred in India within a span of 3 months. To address the confluence of factors that led to the observed imbalance in the death rate relative to other countries, the Sponsor took the following steps to attempt to improve outcomes in patients in India:

- Retrained Investigators in India on the importance of supportive care and the specific supportive care recommendations included in the study protocol.

- Implemented additional safety monitoring BIW, which established a parallel assessment schedule between the SVd and Vd arms.
- Increased communication between Sponsor and study Investigators in India.

After the implementation of the additional measures, no new cases of sepsis or deaths were reported from India.

Table 8: Overview of Deaths and Primary Cause of Death (Safety Population) – Updated Analysis

	SVd Arm (N=195) n (%)	Vd Arm (N=204) n (%)	Total (N=399) n (%)
Total Deaths on Study	68	79[a]	147
Deaths Occurring Within 30 Days of Last Dose of Study Drug[b]	16 (8.2)	18 (8.8)	34 (8.5)
Primary Cause of Death			
PD	3 (1.5)	4 (2.0)	7 (1.8)
AEs	13 (6.7)[g]	14 (6.9)[c]	27 (6.8)
Deaths Occurring After the Crossover and Within 30 Days of Last Dose of Crossover Treatment[d]	NA	14 (6.9)	14 (3.5)
Deaths Occurring After the Crossover and Within 30 Days of Last Dose of Bortezomib in Vd and Within 7 Days of Study Drug in the SVdX/SdX	NA	4 (5.2)	4 (5.2)
Primary Cause of Death			
PD	NA	0	0
AEs	NA	4 (5.2)[e]	4 (5.2)[e]
Deaths Occurring After 30 Days of Last Dose of Study Drug[c]	52 (26.7)	47 (23.0)[f]	99 (24.8)

Data cut-off date: 15 Feb 2021

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; PD=progressive disease; PT=preferred term; SdX=selinexor plus low-dose dexamethasone treatment after crossover; SVd=selinexor with bortezomib and dexamethasone; SVdX=SVd treatment after crossover; TEAE=treatment-emergent adverse event; Vd=bortezomib with dexamethasone.

[a] One additional patient died on the Vd arm, but death occurred before Vd treatment had begun.

b For patients who crossed over, only deaths that occurred within 30 days of the last dose of Vd treatment and before the first dose of selinexor are included.

[c] One patient died due to TEAE in the context of PD and is counted in the TEAE group. Of these 14 patients with deaths due to AEs, in one patient (Patient ID: [redacted]), the event of pneumonia was not considered as treatment-emergent as it occurred after the patient started new anti-cancer treatment and is not reflected in Table 49 (TEAEs leading to death).

[d] For patients who crossed over, only deaths that occurred after the first dose of selinexor and within 30 days of the last dose of SVdX or SdX treatment are included. e Four of the 9 patients with TEAEs leading to death in the crossover arm died within 30 days of the last dose of Vd and within 7 days of SVdX study treatment. Denominator for the group is 74 (all crossover patients).

[f] The number 47 includes 24 patients who died in the crossover arms, 30 days after the last dose of crossover treatment.

[g] In addition to the 13 deaths due to TEAEs within 30 days of last dose of study drug, one patient (Patient ID:[redacted]) had a TEAE leading to death (PT: Pneumonia); the onset date was within 30 days of the last dose of the study drug; but, its outcome of death was reported as occurred 30 days after the last dose of study drug

Table 9: Treatment-Emergent Adverse Events Leading to Death by treatment group – Primary cause of death (Safety Population) – Updated Analysis

MedDRA Preferred Term	All SVd (N=301[a]) n (%)	BOSTON SVd Arm (N=195) n (%)	BOSTON Vd Arm (N=204) n (%)
Patients with at least 1 TEAE leading to death	25 (8.3)	14 (7.2)	13 (6.4)
Pneumonia[b]	4 (1.3)	3 (1.5)	4 (2.0)
Sepsis/Septic shock[c]	5 (1.7)	3 (1.5)	0
Myocardial infarction	3 (1.0)	1 (0.5)	0
Acute kidney injury	1 (0.3)	0	0
Cerebral haemorrhage	2 (0.7)	1 (0.5)	0
Shock haemorrhagic	1 (0.3)	1 (0.5)	0
Bronchitis	1 (0.3)	1 (0.5)	0
Cardiac failure acute	2 (0.7)	1 (0.5)	0
Cerebrovascular accident	1 (0.3)	0	0
Death	1 (0.3)	1 (0.5)	0
Influenza	1 (0.3)	0	0
Injury	1 (0.3)	1 (0.5)	0
Pulmonary oedema	1 (0.3)	1 (0.5)	1 (0.5)
Sudden death	1 (0.3)	0	0
Anaemia[d]	0	0	1 (0.5)
Cardiomyopathy	0	0	1 (0.5)
Circulatory collapse	0	0	1 (0.5)
Left ventricular failure	0	0	1 (0.5)
Myelodysplastic syndrome	0	0	1 (0.5)
Myocardial ischaemia	0	0	1 (0.5)
Respiratory failure	0	0	1 (0.5)
Subdural haemorrhage	0	0	1 (0.5)

Source: Table 14.3.1.8.1.2_updated and Listing 16.2.7.1.4_updated.
Data cut-off date: 15 Feb 2021 (BOSTON); 01 Sep 2019 (STOMP)
MedDRA: Medical Dictionary for Regulatory Activities; SVd: selinexor with bortezomib and dexamethasone; TEAE: treatment-emergent adverse event; Vd: bortezomib and dexamethasone.
Note: This table uses MedDRA version 22.0. Preferred Terms were recoded to aggregate medically similar Preferred Terms.

[a] All SVd population includes 195 patients from the BOSTON SVd arm + 64 patients from the BOSTON crossover arm (SVdX), including 1 additional patient who crossed over from Vd arm since the primary analysis + 42 patients from the supportive study, STOMP.

[b] one patient (BOSTON SVd) also had fatal cardio-respiratory arrest.

[c] one patient (BOSTON SVd) also had multiple organ dysfunction syndrome fatal; another patient (BOSTON SVd) also had pneumonia fatal and acute kidney injury fatal (both cases occurred in India).

Table 10: Results of Activities to Improve Outcomes in India - Primary Analysis

	India SVd Patients with AE Onset < 1 Feb 2019 (N=23)		India SVd Patients Still on Treatment as of 1 Feb 2019 (N=12)		India Vd Patients with AE Onset < 1 Feb 2019 (N=20)		India Vd Patients Still on Treatment as of 1 Feb 2019 (N=11)	
	n	%	N	%	n	%	n	%
TEAE	23	100	12	100	20	100	9	81.8
SAE	13	56.5	3	25.0	7	35.0	0	0
≥Grade 3 AE	17	73.9	6	50.0	14	70.0	4	36.4
Maximum Severity (Grade 3)	12	52.2	5	41.7	12	60.0	3	27.3
Maximum Severity (Grade 4)	1	4.3	1	8.3	2	10.0	1	9.1
Maximum Severity (Grade 5)	4	17.4	0	0	0	0	0	0

Source: Table 14.3.1.1.13.5.2, Table 14.3.1.1.13.5.3.
Data cut-off date: 18 Feb 2020
AE=adverse event; SAE=serious adverse event; SVd=selinexor with bortezomib and dexamethasone; TEAE=treatment-emergent adverse event; Vd=bortezomib with dexamethasone.

In the **crossover population**, 13 (20.3%) patients in the SVdX arm and 1 (7.7%) patient in the SdX arm died after crossing over from the Vd arm and within 30 days of the last dose of study drug (SVdX or SdX). In total, 9 (14.1%) patients in the SVdX arm and 1 (7.7%) patient in the SdX arm experienced TEAEs leading to death after crossover.

Table 11: Overview of Deaths and Primary Cause of Death (Crossover Population) – Updated Analysis

	SVdX Arm (N =64) n (%)	SdX Arm (N=13) n (%)
Deaths Occurring Within 30 Days of Last Dose of Study Drug	13 (20.3)	1 (7.7)
Primary Cause of Death		
PD	4 (6.3)	0
Adverse Events	9 (14.1)[a]	1 (7.7)[a]
TEAEs Leading to Death After the Crossover and Within 30 Days of Last Dose of Bortezomib in Vd and Within 7 Days of Study Drug in the SVdX/SdX	4 (6.3)[b]	0 (0)
Deaths Occurring After 30 Days of Last Dose of Study Drug	22 (34.4)	2 (15.4)

Source: Table 14.3.2.2.1_updated, Listing 16.2.1.1_updated.
Data cut-off date: 15 Feb 2021
PD=progressive disease; PT=preferred term; SdX=selinexor plus low-dose dexamethasone treatment after crossover; SVdX=SVd treatment after crossover; TEAE=treatment-emergent adverse event.
Note: Only death events that occurred after the crossover to the SVdX or SdX treatment are included.
[a] The Investigator reported that 1 patient died due to PD and TEAE in each arm (SVdX and SdX). To be conservative, the Sponsor counted these as TEAEs.
[b] Four of the 8 patients with TEAEs leading to death in the SVdX arm died within 30 days of the last dose of Vd and within 7 days of SVdX study treatment.

Serious adverse events

Table 12: Treatment-Emergent Serious Adverse Events occurring in ≥2% of Patients in the All SVd Population, Safety Population – Updated Analysis

MedDRA System Organ Class MedDRA Preferred Term	All SVd (N=301[a]) n (%)	BOSTON SVd Arm (N=195) n (%)	BOSTON Vd Arm (N=204) n (%)
Patients with at least 1 treatment-emergent SAE	148 (49.2)	106 (54.4)	79 (38.7)
Blood and lymphatic system disorders	15 (5.0)	9 (4.6)	5 (2.5)
Anaemia	9 (3.0)	6 (3.1)	3 (1.5)
Thrombocytopenia	6 (2.0)	3 (1.5)	1 (0.5)
Eye disorders	12 (4.0)	9 (4.6)	0
Cataract	11 (3.7)	9 (4.6)	0
Gastrointestinal disorders	26 (8.6)	18 (9.2)	4 (2.0)
Diarrhoea	9 (3.0)	7 (3.6)	0
Vomiting	9 (3.0)	7 (3.6)	0
Nausea	7 (2.3)	4 (2.1)	0
Infections and infestations	75 (24.9)	54 (27.7)	40 (19.6)
Pneumonia[c]	38 (12.6)	29 (14.9)	27 (13.2)
Sepsis[c]	10 (3.3)	8 (4.1)	2 (1.0)
Urinary tract infection	6 (2.0)	4 (2.1)	0
Renal and urinary disorders	8 (2.7)	5 (2.6)	2 (1.0)
Acute kidney injury	7 (2.3)	4 (2.1)	2 (1.0)

Source: Table 14.3.1.4.1.1_updated, Table 14.3.1.4.1.2_updated, Table 14.3.2.1.1.7_updated, and Table 14.3.2.1.1.8_updated.
Data cut-off date: 15 Feb 2021 (BOSTON); 01 Sep 2019 (STOMP)
Note: This table uses MedDRA version 22.0. System Organ Classes were recoded to aggregate medically similar SOCs. Preferred Terms were recoded to aggregate medically similar PTs.
MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SAE: serious adverse event; SOC: system organ class; SVd: selinexor with bortezomib and dexamethasone; Vd: bortezomib and dexamethasone.
[a] All SVd population includes 195 patients from the BOSTON SVd arm + 64 patients from the BOSTON crossover arm (SVdX), including 1 additional patient who crossed over from the Vd arm since the primary analysis + 42 patients from the supportive study, STOMP.
[b] includes all PTs from pneumonia Customized MedDRA Query (see Section 3.1.5.3.1).
[c] includes all PTs from sepsis Customized MedDRA Query (Table 14.3.2.1.1.8).

Other significant adverse events

Table 13: Adverse Event of Clinical Interest Categories

Group Category	AECI Category
Cytopenias	Thrombocytopenia
	Neutropenia
Gastrointestinal events	Nausea/vomiting
	Decreased appetite/decreased weight
Infection and infestation events	Pneumonia
	Sepsis
	Opportunistic infection
Eye disorders events	Blurred vision
	Cataract
Metabolism and nutrition disorders	Hyponatremia
Nervous system disorders	Neurological toxicity
Hepatic events	Hepatobiliary disorders
Cardiac events	Cardiac toxicity

Cytopenias

Thrombocytopenia

As of the updated analysis, the incidence of SMQ of thrombocytopenia was comparable in the All SVd population and BOSTON SVd arm (58.5% and 62.1%, respectively) and was higher than the BOSTON Vd arm (27.5%). The incidence of Grade 3/4 TEAEs and Grade 4 TEAEs of thrombocytopenia was higher in All SVd population and BOSTON SVd arm (Grade 3/4: 39.9% and 40.5%; Grade 4: 15.6% and 11.3%, respectively) compared with BOSTON Vd arm (Grade 3/4: 17.6%; Grade 4: 6.9%). Since the primary analysis, 4, 2, and 1 additional patient reported Grade 3/4 TEAEs; and 1, 1, and 0 additional patients reported Grade 4 TEAEs in All SVd population, BOSTON SVd arm, and BOSTON Vd arm, respectively. The Grade 4 TEAE reported in the BOSTON SVd arm was not associated with any Grade ≥3 bleeding events. The incidence of SAEs and discontinuations due to thrombocytopenia was low across all arms (SAEs: 2.0%, 1.5%, and 0.5% and discontinuations: 2.7%, 2.1%, and 0.5%, in All SVd population, BOSTON SVd arm, and BOSTON Vd arm, respectively) with no change in the incidence in any of the groups since primary analysis. The majority of the TEAEs were managed by dose modifications (36.9%, 40.0%, and 9.8%, in All SVd population, BOSTON SVd arm, and BOSTON Vd arm, respectively). In the ALL SVd population, BOSTON SVd arm, and the BOSTON Vd arm, the incidence of Grade ≥3 bleeding events among the patients with Grade ≥3 thrombocytopenia was same as the primary analysis (5.0%, 5.1% and 5.6%, respectively).

Table 14: Summary of Thrombocytopenia (Safety Population) – Updated Analysis

Patients with at least 1	All SVd (N=301[a]) n (%)	BOSTON SVd Arm (N=195) n (%)	BOSTON Vd Arm (N=204) n (%)
Treatment-emergent TEAE	176 (58.5)	121 (62.1)	56 (27.5)
Grade 3/4 TEAE[b]	120 (39.9)	79 (40.5)	36 (17.6)
Grade 4 TEAE[b]	47 (15.6)	22 (11.3)	14 (6.9)
Treatment-emergent SAE	6 (2.0)	3 (1.5)	1 (0.5)
TEAE leading to dose modification in any study treatment[c, d]	111 (36.9)	78 (40.0)	20 (9.8)
TEAE leading to dose reduction in any study treatment	86 (28.6)	65 (33.3)	9 (4.4)
TEAE leading to dose interruption in any study treatment	98 (32.6)	69 (35.4)	16 (7.8)
TEAE leading to study treatment discontinuation	8 (2.7)	4 (2.1)	1 (0.5)
TEAE leading to death	0	0	0

Source: Table 14.3.2.1.1.1_Updated.
Data cut-off date: 15 Feb 2021 (BOSTON); 01 Sep 2019 (STOMP)
SVd: selinexor with bortezomib and dexamethasone; TEAE: treatment-emergent adverse event;
TRAE: treatment-related adverse event; Vd: bortezomib and dexamethasone.

[a] All SVd population includes 195 patients from the BOSTON SVd arm + 64 patients from the BOSTON crossover arm (SVdX), including 1 additional patient who crossed over from the Vd arm since the primary analysis + 42 patients from the supportive study, STOMP.

[b] Based on maximum severity grade of each patient.

[c] The number of patients with dose modification(s) was not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.

[d] Study treatment was selinexor with bortezomib and dexamethasone for SVd arm, and bortezomib with dexamethasone for Vd arm.

Neutropenia

Table 15: Summary of Neutropenia, Safety Population – Updated Analysis

Patients with at least 1	All SVd (N=301[a]) n (%)	BOSTON SVd Arm (N=195) n (%)	BOSTON Vd Arm (N=204) n (%)
Treatment-emergent adverse event	61 (20.3)	31 (15.9)	14 (6.9)
Grade 3/4 TEAE[b]	41 (13.6)	19 (9.7)	8 (3.9)
Grade 4 TEAE[b]	8 (2.7)	5 (2.6)	3 (1.5)
Treatment-emergent SAE	4 (1.3)	2 (1.0)	1 (0.5)
TEAE leading to dose modification in any study treatment[c,d]	29 (9.6)	18 (9.2)	3 (1.5)
TEAE leading to dose reduction in any study treatment	14 (4.7)	9 (4.6)	0
TEAE leading to dose interruption in any study treatment	28 (9.3)	18 (9.2)	3 (1.5)
TEAE leading to study treatment discontinuation	1 (0.3)	0	0
TEAE leading to death	0	0	0

Source: Table 14.3.2.1.1.2_updated.
Data cut-off date: 15 Feb 2021 (BOSTON); 01 Sep 2019 (STOMP)
SAE: adverse event; SVd: selinexor with bortezomib and dexamethasone, TEAE: treatment-emergent adverse event; TRAE: treatment-related adverse event Vd: bortezomib and dexamethasone.
[a] All SVd population includes 195 patients from the BOSTON SVd arm + 64 patients from the BOSTON crossover arm (SVdX), including 1 additional patient who crossed over from the Vd arm since the primary analysis + 42 patients from the supportive study, STOMP.
[b] Based on maximum severity grade of each patient.
[c] The number of patients with dose modification(s) was not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.
[d] Study treatment was selinexor with bortezomib and dexamethasone for SVd arm, and bortezomib with dexamethasone for Vd arm.

Gastrointestinal events

Nausea/vomiting

The incidence of nausea and vomiting based on updated analysis was same as the primary analysis in All SVD population and BOSTON SVd arm; 1 additional patient reported TEAE of nausea and vomiting each in Vd arm since the primary analysis. No new ≥Grade 3 TEAEs, dose modifications due to AEs, SAEs, or discontinuations due to nausea or vomiting were reported in either arms since the primary analysis and the incidence of these events was same as the primary analysis.

Table 16: Summary of Nausea, Safety Population –Updated Analysis

Patients with at Least One	All SVd (N = 301) n (%)	BOSTON SVd Arm (N = 195) n (%)	BOSTON Vd Arm (N = 204) n (%)
Treatment-Emergent Adverse Event	150 (49.8)	98 (50.3)	21 (10.3)
Grade 3/4 TEAE [1]	20 (6.6)	15 (7.7)	0
Grade 4 TEAE [1]	0	0	0
Serious TEAE	7 (2.3)	4 (2.1)	0
TEAE Leading to Dose Modification in Any Study Treatment [2] [3]	35 (11.6)	21 (10.8)	0
TEAE Leading tp Dose Reduction in Any Study Treatment	22 (7.3)	14 (7.2)	0
TEAE Leading to Dose Interruption in Any Study Treatment	22 (7.3)	14 (7.2)	0
TEAE Leading to Study Treatment Discontinuation	9 (3.0)	6 (3.1)	0
TEAE Leading to Death	0	0	0
Treatment-Emergent Treatment-Related Adverse Event [4]	142 (47.2)	93 (47.7)	12 (5.9)
Grade 3/4 TRAE [1]	20 (6.6)	15 (7.7)	0
Grade 4 TRAE [1]	0	0	0
Serious TRAE	7 (2.3)	4 (2.1)	0
TRAE Leading to Dose Modification in Any Study Treatment [2] [3]	34 (11.3)	20 (10.3)	0
TRAE Leading to Dose Reduction in Any Study Treatment	22 (7.3)	14 (7.2)	0
TRAE Leading to Dose Interruption in Any Study Treatment	21 (7.0)	13 (6.7)	0
TRAE Leading to Study Treatment Discontinuation	9 (3.0)	6 (3.1)	0
TRAE Leading to Death	0	0	0

(Database Cutoff Date: 2021-02-15; Source Data: ADAE, ADDENOM) Executed: 2021-03-09 12:24
[1] Based on maximum severity grade of each patient.
[2] The number of patients with dose modification(s) is not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.
[3] Study treatment is selinexor with bortezomib and dexamethasone for SVd Arm, and bortezomib with dexamethasone for Vd Arm.
[4] An AE is considered treatment-related if it is selinexor-related and/or bortezomib-related and/or dexamethasone-related.

Table 17: Summary of Vomiting, Safety Population – Updated analysis

Patients with at Least One	All SVd (N = 301) n (%)	BOSTON SVd Arm (N = 195) n (%)	BOSTON Vd Arm (N = 204) n (%)
Treatment-Emergent Adverse Event	69 (22.9)	40 (20.5)	10 (4.9)
Grade 3/4 TEAE [1]	11 (3.7)	8 (4.1)	0
Grade 4 TEAE [1]	0	0	0
Serious TEAE	9 (3.0)	7 (3.6)	0
TEAE Leading to Dose Modification in Any Study Treatment [2] [3]	14 (4.7)	9 (4.6)	1 (0.5)
TEAE Leading to Dose Reduction in Any Study Treatment	9 (3.0)	6 (3.1)	1 (0.5)
TEAE Leading to Dose Interruption in Any Study Treatment	9 (3.0)	6 (3.1)	0
TEAE Leading to Study Treatment Discontinuation	4 (1.3)	4 (2.1)	0
TEAE Leading to Death	0	0	0
Treatment-Emergent Treatment-Related Adverse Event [4]	57 (18.9)	34 (17.4)	5 (2.5)
Grade 3/4 TRAE [1]	11 (3.7)	8 (4.1)	0
Grade 4 TRAE [1]	0	0	0
Serious TRAE	9 (3.0)	7 (3.6)	0

Patients with at Least One	All SVd (N = 301) n (%)	BOSTON SVd Arm (N = 195) n (%)	BOSTON Vd Arm (N = 204) n (%)
TRAE Leading to Dose Modification in Any Study Treatment [2] [3]	12 (4.0)	8 (4.1)	1 (0.5)
TRAE Leading to Dose Reduction in Any Study Treatment	9 (3.0)	6 (3.1)	1 (0.5)
TRAE Leading to Dose Interruption in Any Study Treatment	6 (2.0)	4 (2.1)	0
TRAE Leading to Study Treatment Discontinuation	4 (1.3)	4 (2.1)	0
TRAE Leading to Death	0	0	0

(Database Cutoff Date: 2021-02-15; Source Data: ADAE, ADDENOM) Executed: 2021-03-09 12:24
[1] Based on maximum severity grade of each patient.
[2] The number of patients with dose modification(s) is not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.
[3] Study treatment is selinexor with bortezomib and dexamethasone for SVd Arm, and bortezomib with dexamethasone for Vd Arm.
[4] An AE is considered treatment-related if it is selinexor-related and/or bortezomib-related and/or dexamethasone-related.

Decreased appetite/weight decreased

For the TEAE of decreased appetite, there was no change in the incidence of TEAEs, Grade 3 TEAEs, SAEs, TEAEs leading to dose modifications, and TEAEs leading to discontinuation compared with the primary analysis in all 3 groups. No Grade 4 TEAEs or deaths were reported in any of the 3 groups.

For the TEAE of decreased weight, the incidence of all TEAEs, SAEs, TEAEs leading to dose modifications, or discontinuations of treatment was similar to the primary analysis in all 3 groups. One additional patient reported a Grade 3 TEAE of weight decreased in the All SVd population and BOSTON SVd arm since the primary analysis. No Grade 4 TEAEs or deaths were reported in any of the 3 groups.

Decreased appetite

Table 18: Summary of Decreased Appetite, Safety Population – Updated analysis

Patients with at Least One	All SVd (N = 301) n (%)	BOSTON SVd Arm (N = 195) n (%)	BOSTON Vd Arm (N = 204) n (%)
Treatment-Emergent Adverse Event	112 (37.2)	69 (35.4)	11 (5.4)
Grade 3/4 TEAE [1]	10 (3.3)	7 (3.6)	0
Grade 4 TEAE [1]	0	0	0
Serious TEAE	2 (0.7)	1 (0.5)	0
TEAE Leading to Dose Modification in Any Study Treatment [2] [3]	36 (12.0)	27 (13.8)	2 (1.0)
TEAE Leading to Dose Reduction in Any Study Treatment	19 (6.3)	17 (8.7)	0
TEAE Leading to Dose Interruption in Any Study Treatment	26 (8.6)	18 (9.2)	2 (1.0)
TEAE Leading to Study Treatment Discontinuation	6 (2.0)	4 (2.1)	1 (0.5)
TEAE Leading to Death	0	0	0
Treatment-Emergent Treatment-Related Adverse Event [4]	103 (34.2)	63 (32.3)	8 (3.9)
Grade 3/4 TRAE [1]	10 (3.3)	7 (3.6)	0
Grade 4 TRAE [1]	0	0	0

Patients with at Least One	All SVd (N = 301) n (%)	BOSTON SVd Arm (N = 195) n (%)	BOSTON Vd Arm (N = 204) n (%)
Serious TRAE	2 (0.7)	1 (0.5)	0
TRAE Leading to Dose Modification in Any Study Treatment [2] [3]	34 (11.3)	26 (13.3)	1 (0.5)
TRAE Leading to Dose Reduction in Any Study Treatment	16 (5.3)	15 (7.7)	0
TRAE Leading to Dose Interruption in Any Study Treatment	25 (8.3)	17 (8.7)	1 (0.5)
TRAE Leading to Study Treatment Discontinuation	6 (2.0)	4 (2.1)	1 (0.5)
TRAE Leading to Death	0	0	0

(Database Cutoff Date: 2021-02-15; Source Data: ADAE, ADDENOM) Executed: 2021-03-09 12:24
[1] Based on maximum severity grade of each patient.
[2] The number of patients with dose modification(s) is not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.
[3] Study treatment is selinexor with bortezomib and dexamethasone for SVd Arm, and bortezomib with dexamethasone for Vd Arm.
[4] An AE is considered treatment-related if it is selinexor-related and/or bortezomib-related and/or dexamethasone-related.

Decreased weight

Table 19: Summary of Decreased Weight, Safety Population – Updated analysis

Patients with at Least One	All SVd (N = 301) n (%)	BOSTON SVd Arm (N = 195) n (%)	BOSTON Vd Arm (N = 204) n (%)
Treatment-Emergent Adverse Event	85 (28.2)	51 (26.2)	25 (12.3)
Grade 3/4 TEAE [1]	6 (2.0)	5 (2.6)	2 (1.0)
Grade 4 TEAE [1]	0	0	0
Serious TEAE	0	0	0
TEAE Leading to Dose Modification in Any Study Treatment [2] [3]	27 (9.0)	19 (9.7)	5 (2.5)
TEAE Leading to Dose Reduction in Any Study Treatment	20 (6.6)	14 (7.2)	4 (2.0)
TEAE Leading to Dose Interruption in Any Study Treatment	18 (6.0)	12 (6.2)	2 (1.0)
TEAE Leading to Study Treatment Discontinuation	3 (1.0)	2 (1.0)	1 (0.5)
TEAE Leading to Death	0	0	0
Treatment-Emergent Treatment-Related Adverse Event [4]	65 (21.6)	38 (19.5)	8 (3.9)
Grade 3/4 TRAE [1]	3 (1.0)	3 (1.5)	0
Grade 4 TRAE [1]	0	0	0
Serious TRAE	0	0	0
TRAE Leading to Dose Modification in Any Study Treatment [2] [3]	23 (7.6)	18 (9.2)	3 (1.5)
TRAE Leading to Dose Reduction in Any Study Treatment	18 (6.0)	14 (7.2)	2 (1.0)
TRAE Leading to Dose Interruption in Any Study Treatment	15 (5.0)	11 (5.6)	1 (0.5)
TRAE Leading to Study Treatment Discontinuation	2 (0.7)	2 (1.0)	0
TRAE Leading to Death	0	0	0

(Database Cutoff Date: 2021-02-15; Source Data: ADAE, ADDENOM) Executed: 2021-03-09 12:25
[1] Based on maximum severity grade of each patient.
[2] The number of patients with dose modification(s) is not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.
[3] Study treatment is selinexor with bortezomib and dexamethasone for SVd Arm, and bortezomib with dexamethasone for Vd Arm.
[4] An AE is considered treatment-related if it is selinexor-related and/or bortezomib-related and/or dexamethasone-related.

<u>Infection ad infestation events</u>

Pneumonia

Table 20: Summary of Pneumonia, Safety Population – Updated Analysis

Patients With At Least 1	All SVd (N=301[a]) n (%)	BOSTON SVd Arm (N=195) n (%)	BOSTON Vd Arm (N=204) n (%)
Treatment-emergent adverse event	49 (16.3)	37 (19.0)	35 (17.2)
Grade 3/4 TEAE[b]	31 (10.3)	24 (12.3)	21 (10.3)
Grade 4 TEAEb[b]	4 (1.3)	2 (1.0)	0
Treatment-emergent SAE	38 (12.6)	29 (14.9)	27 (13.2)
TEAE leading to dose modification in any study treatment[c, d]	37 (12.3)	28 (14.4)	27 (13.2)
TEAE leading to dose reduction in any study treatment	8 (2.7)	8 (4.1)	2 (1.0)
TEAE leading to dose interruption in any study treatment	37 (12.3)	28 (14.4)	27 (13.2)
TEAE leading to study treatment discontinuation	3 (1.0)	1 (0.5)	0
TEAE leading to death	5 (1.7)	4 (2.1)	4 (2.0)

Source: Table 14.3.2.1.1.7_updated.
Data cut-off date: 15 Feb 2021 (BOSTON); 01 Sep 2019 (STOMP)
SAE: serious adverse event; SVd: selinexor plus bortezomib plus low-dose dexamethasone; TEAE: treatment emergent adverse event; TRAE: treatment-related adverse event; Vd: bortezomib plus low-dose dexamethasone.

[a] All SVd population includes 195 patients from the BOSTON SVd arm + 64 patients from the BOSTON crossover arm (SVdX), including 1 additional patient who crossed over from Vd arm since the primary analysis + 42 patients from the supportive study, STOMP.

[b] Based on maximum severity grade of each patient.

[c] The number of patients with dose modification(s) was not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.

[d] Study treatment was selinexor with bortezomib and dexamethasone for SVd arm, and bortezomib with dexamethasone for Vd arm.

Sepsis

In the updated analysis the incidence of CMQ of sepsis in all 3 groups was similar to the primary analysis and no new patients reported events of sepsis, including Grade 3/4 events, SAEs, events leading to dose modifications or dose discontinuations, and deaths due to sepsis since the primary analysis.

Table 21: Summary of Sepsis, Safety Population – Updated analysis

Patients with at Least One	All SVd (N = 301) n (%)	BOSTON SVd Arm (N = 195) n (%)	BOSTON Vd Arm (N = 204) n (%)
Treatment-Emergent Adverse Event	11 (3.7)	8 (4.1)	2 (1.0)
Grade 3/4 TEAE [1]	5 (1.7)	5 (2.6)	2 (1.0)
Grade 4 TEAE [1]	4 (1.3)	4 (2.1)	0
Serious TEAE	10 (3.3)	8 (4.1)	2 (1.0)
TEAE Leading to Dose Modification in Any Study Treatment [2] [3]	5 (1.7)	4 (2.1)	1 (0.5)
TEAE Leading to Dose Reduction in Any Study Treatment	0	0	1 (0.5)
TEAE Leading to Dose Interruption in Any Study Treatment	5 (1.7)	4 (2.1)	1 (0.5)
TEAE Leading to Study Treatment Discontinuation	1 (0.3)	1 (0.5)	0
TEAE Leading to Death	5 (1.7)	3 (1.5)	0
Treatment-Emergent Treatment-Related Adverse Event [4]	8 (2.7)	5 (2.6)	1 (0.5)
Grade 3/4 TRAE [1]	3 (1.0)	3 (1.5)	1 (0.5)
Grade 4 TRAE [1]	2 (0.7)	2 (1.0)	0
Serious TRAE	7 (2.3)	5 (2.6)	1 (0.5)
TRAE Leading to Dose Modification in Any Study Treatment [2] [3]	3 (1.0)	2 (1.0)	1 (0.5)
TRAE Leading to Dose Reduction in Any Study Treatment	0	0	1 (0.5)
TRAE Leading to Dose Interruption in Any Study Treatment	3 (1.0)	2 (1.0)	1 (0.5)
TRAE Leading to Study Treatment Discontinuation	1 (0.3)	1 (0.5)	0
TRAE Leading to Death	4 (1.3)	2 (1.0)	0

(Database Cutoff Date: 2021-02-15; Source Data: ADAE, ADDENOM) Executed: 2021-03-09 12:25
[1] Based on maximum severity grade of each patient.
[2] The number of patients with dose modification(s) is not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.
[3] Study treatment is selinexor with bortezomib and dexamethasone for SVd Arm, and bortezomib with dexamethasone for Vd Arm.
[4] An AE is considered treatment-related if it is selinexor-related and/or bortezomib-related and/or dexamethasone-related.
F:\Biostatistics\KPT-330\ISS_BOSTON\Data_Cuts\2021-02-15\Dev\MAA_Update\T-14-3-2-1-1-8-AE-Summary-by-Treatment-Group-Safety-Sepsis-CMQ-updated.sas

Opportunistic infection

Table 22: Summary of Opportunistic Infection, Safety Population – Updated analysis

Patients with at Least One	All SVd (N = 301) n (%)	BOSTON SVd Arm (N = 195) n (%)	BOSTON Vd Arm (N = 204) n (%)
Treatment-Emergent Adverse Event	24 (8.0)	16 (8.2)	9 (4.4)
Grade 3/4 TEAE [1]	6 (2.0)	5 (2.6)	3 (1.5)
Grade 4 TEAE [1]	1 (0.3)	1 (0.5)	0
Serious TEAE	4 (1.3)	3 (1.5)	2 (1.0)
TEAE Leading to Dose Modification in Any Study Treatment [2] [3]	12 (4.0)	9 (4.6)	6 (2.9)
TEAE Leading to Dose Reduction in Any Study Treatment	1 (0.3)	1 (0.5)	0
TEAE Leading to Dose Interruption in Any Study Treatment	12 (4.0)	9 (4.6)	6 (2.9)
TEAE Leading to Study Treatment Discontinuation	0	0	1 (0.5)
TEAE Leading to Death	0	0	0
Treatment-Emergent Treatment-Related Adverse Event [4]	12 (4.0)	8 (4.1)	5 (2.5)
Grade 3/4 TRAE [1]	3 (1.0)	2 (1.0)	2 (1.0)
Grade 4 TRAE [1]	1 (0.3)	1 (0.5)	0

Patients with at Least One	All SVd (N = 301) n (%)	BOSTON SVd Arm (N = 195) n (%)	BOSTON Vd Arm (N = 204) n (%)
Serious TRAE	2 (0.7)	1 (0.5)	1 (0.5)
TRAE Leading to Dose Modification in Any Study Treatment [2] [3]	5 (1.7)	4 (2.1)	3 (1.5)
TRAE Leading to Dose Reduction in Any Study Treatment	0	0	0
TRAE Leading to Dose Interruption in Any Study Treatment	5 (1.7)	4 (2.1)	3 (1.5)
TRAE Leading to Study Treatment Discontinuation	0	0	1 (0.5)
TRAE Leading to Death	0	0	0

(Database Cutoff Date: 2021-02-15; Source Data: ADAE, ADDENOM) Executed: 2021-03-09 12:26
[1] Based on maximum severity grade of each patient.
[2] The number of patients with dose modification(s) is not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.
[3] Study treatment is selinexor with bortezomib and dexamethasone for SVd Arm, and bortezomib with dexamethasone for Vd Arm.
[4] An AE is considered treatment-related if it is selinexor-related and/or bortezomib-related and/or dexamethasone-related.

Eye disorders events

Blurred vision

The incidence of blurred vision (CMQ) was comparable in the All SVd population and BOSTON SVd arm and higher than the BOSTON Vd arm (13.0%, 13.8%, 7.4%, respectively).

Table 23: Summary of Blurred Vision, Safety Population – Updated Analysis

Patients With At Least One	All SVd (N=301[a]) n (%)	BOSTON SVd Arm (N=195) n (%)	BOSTON Vd Arm (N=204) n (%)
Treatment-emergent adverse event	39 (13.0)	27 (13.8)	15 (7.4)
Grade 3/4 TEAE[b]	3 (1.0)	2 (1.0)	0
Grade 4 TEAE[b]	0	0	0
Treatment-emergent SAE	0	0	0
TEAE leading to dose modification in any study treatment[c,d]	6 (2.0)	3 (1.5)	2 (1.0)
TEAE leading to dose reduction in any study treatment	4 (1.3)	2 (1.0)	1 (0.5)
TEAE leading to dose interruption in any study treatment	4 (1.3)	2 (1.0)	1 (0.5)
TEAE leading to study treatment discontinuation	0	0	0
TEAE leading to death	0	0	0

Source: Table 14.3.2.1.1.10_updated.
Data cut-off date: 15 Feb 2021 (BOSTON); 01 Sep 2019 (STOMP)
SAE: adverse event; SVd: selinexor with bortezomib and dexamethasone, TEAE: treatment-emergent adverse event; TRAE: treatment-related adverse event Vd: bortezomib and dexamethasone.
[a] All SVd population includes 195 patients from the BOSTON SVd arm + 64 patients from the BOSTON crossover arm (SVdX), including 1 additional patient who crossed over from Vd arm since the primary analysis + 42 patients from the supportive study, STOMP.
[b] Based on maximum severity grade of each patient.
[c] The number of patients with dose modification(s) was not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.
[d] Study treatment was selinexor with bortezomib and dexamethasone for SVd arm, and bortezomib with dexamethasone for Vd arm.

Cataract

In the BOSTON study, 386 of 399 patients in the Safety Population had a screening OE. At baseline, 120 (61.5%) patients on the SVd arm and 130 (63.7%) patients on the Vd arm had cataract on OE.

Based on OE, occurrence of new cataracts was seen in 19 (25.3%) in the BOSTON SVd arm and 10 (12.2%) patients on the BOSTON Vd arm with 1 additional patient in BOSTON SVd arm and 3

additional patients in BOSTON Vd arm developing new-onset cataracts per OE since the primary analysis.

Worsening of cataracts (identified based on reported TEAEs of cataract) was noted in 27/117 (23.1%) patients with no ongoing cataract at baseline in the SVd arm versus 10/127 (7.9%) patients in the Vd arm.

Table 24: Summary of Cataract, Safety Population – Updated Analysis

Patients With At Least 1	All SVd (N=301[a]) n (%)	BOSTON SVd Arm (N=195) n (%)	BOSTON Vd Arm (N=204) n (%)
Treatment-emergent adverse event	67 (22.3)	46 (23.6)[b]	15 (7.4)[b]
Grade 3/4 TEAE[c]	30 (10.0)	22 (11.3)	4 (2.0)
Grade 4 TEAE[c]	4 (1.3)	2 (1.0)	3 (1.5)
Treatment-emergent SAE	11 (3.7)	9 (4.6)	0
TEAE leading to dose modification in any study treatment[d, e]	13 (4.3)	11 (5.6)	1 (0.5)
TEAE leading to dose reduction in any study treatment	5 (1.7)	5 (2.6)	1 (0.5)
TEAE leading to dose interruption in any study treatment	10 (3.3)	8 (4.1)	0
TEAE leading to study treatment discontinuation	0	0	0
TEAE leading to death	0	0	0

Source: Table 14.3.2.1.1.11_updated.
Data cut-off date: 15 Feb 2021 (BOSTON); 01 Sep 2019 (STOMP)
SAE: adverse event; SVd: selinexor with bortezomib and dexamethasone, TEAE: treatment-emergent adverse event; TRAE: treatment-related adverse event Vd: bortezomib and dexamethasone.

[a] All SVd population includes 195 patients from the BOSTON SVd arm + 64 patients from the BOSTON crossover arm (SVdX), including 1 additional patient who crossed over from Vd arm since the primary analysis + 42 patients from the supportive study, STOMP.

[b] Per ophthalmology examination (OE); onset of new cataracts was seen in 25.3% of the patients on BOSTON SVd arm versus 12.2% on the BOSTON Vd arm (Module 5.3.5.1, KCP-330-023 CSR, Table 14.3.9.1.1_updated). Worsening of cataract on study was noted in 23.1% of the patients on SVd arm versus 7.9% on the Vd arm (Module 5.3.5.1, KCP-330-023 CSR, Table 14.3.1.1.13.6.1_updated).

[c] Based on maximum severity grade of each patient.

[d] The number of patients with dose modification(s) was not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.

[e] Study treatment was selinexor with bortezomib and dexamethasone for SVd Arm, and bortezomib with dexamethasone for Vd arm.

Hyponatremia

The SMQ of hyponatremia retrieved the PTs of hyponatremia and brain oedema.

Table 25: Summary of hyponatremia, Safety population – Updated analysis

Patients with at Least One	All SVd (N = 301) n (%)	BOSTON SVd Arm (N = 195) n (%)	BOSTON Vd Arm (N = 204) n (%)
Treatment-Emergent Adverse Event	24 (8.0)	16 (8.2)	3 (1.5)
Grade 3/4 TEAE [1]	17 (5.6)	10 (5.1)	1 (0.5)
Grade 4 TEAE [1]	1 (0.3)	1 (0.5)	0
Serious TEAE	1 (0.3)	1 (0.5)	0
TEAE Leading to Dose Modification in Any Study Treatment [2] [3]	4 (1.3)	2 (1.0)	1 (0.5)
TEAE Leading to Dose Reduction in Any Study Treatment	3 (1.0)	2 (1.0)	0
TEAE Leading to Dose Interruption in Any Study Treatment	2 (0.7)	1 (0.5)	1 (0.5)
TEAE Leading to Study Treatment Discontinuation	0	0	0
TEAE Leading to Death	0	0	0
Treatment-Emergent Treatment-Related Adverse Event [4]	20 (6.6)	13 (6.7)	2 (1.0)
Grade 3/4 TRAE [1]	14 (4.7)	8 (4.1)	0
Grade 4 TRAE [1]	0	0	0
Serious TRAE	0	0	0
TRAE Leading to Dose Modification in Any Study Treatment [2] [3]	4 (1.3)	2 (1.0)	0
TRAE Leading to Dose Reduction in Any Study Treatment	3 (1.0)	2 (1.0)	0
TRAE Leading to Dose Interruption in Any Study Treatment	2 (0.7)	1 (0.5)	0
TRAE Leading to Study Treatment Discontinuation	0	0	0
TRAE Leading to Death	0	0	0

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[1] Based on maximum severity grade of each patient.
[2] The number of patients with dose modification(s) is not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.
[3] Study treatment is selinexor with bortezomib and dexamethasone for SVd Arm, and bortezomib with dexamethasone for Vd Arm.
[4] An AE is considered treatment-related if it is selinexor-related and/or bortezomib-related and/or dexamethasone-related.

Nervous system disorders

The CMQ neurological toxicity retrieved following PTs: amnesia, cognitive disorder, confusional state, delirium, depressed level of consciousness, dizziness, encephalopathy, hypersomnia, somnolence, and syncope. Peripheral neuropathy was not included.

The incidence of neurological toxicity (CMQ) was similar in the All SVd population and BOSTON SVd arm and higher than the BOSTON Vd arm (All TEAEs: 24.6%, 24.6%, 7.8%; and Grade 3: 5.0%, 4.1%, and 1.0% respectively); 1 additional patient in the All SVd population and BOSTON SVd arm (and none in the BOSTON Vd arm) reported TEAEs of neurological toxicity (PT: delirium; Grade 3, lasting 36 days and assessed as unrelated to any of the study treatments) since the primary analysis. No Grade 4 events were reported in either arm. The incidence of SAEs and discontinuations of neurological toxicity was low and was comparable across all 3 groups (SAEs: 2.0%, 1.5% and 0.5%, respectively; discontinuation: 3.0%, 2.1% and 1.0% in All SVd population, BOSTON SVd arm and BOSTON Vd arm, respectively); 1 additional patient reported an SAE in All SVd population and BOSTON SVd arm since the primary analysis. There were no new patients with discontinuation of study treatment due to TEAE of neurological toxicity since the primary analysis. There were no deaths due to TEAEs of neurological toxicity

Table 21: Summary of Neurological Toxicity, Safety Population – Updated Analysis

Patients With At Least 1	All SVd (N=301[a]) n (%)	BOSTON SVd Arm (N=195) n (%)	BOSTON Vd Arm (N=204) n (%)
Treatment-emergent adverse event	74 (24.6)	48 (24.6)	16 (7.8)
Grade 3/4 TEAE[b]	15 (5.0)	8 (4.1)	2 (1.0)
Grade 4 TEAE[b]	0	0	0
Treatment-emergent SAE	6 (2.0)	3 (1.5)	1 (0.5)
TEAE leading to dose modification in any study treatment[c,d]	24 (8.0)	15 (7.7)	3 (1.5)
TEAE leading to dose reduction in any study treatment	14 (4.7)	9 (4.6)	1 (0.5)
TEAE leading to dose interruption in any study treatment	17 (5.6)	12 (6.2)	3 (1.5)
TEAE leading to study treatment discontinuation	9 (3.0)	4 (2.1)	2 (1.0)
TEAE leading to death	0	0	0

Source: Table 14.3.2.1.1.13_updated.
Data cut-off date: 15 Feb 2021 (BOSTON); 01 Sep 2019 (STOMP)
SAE: adverse event; SVd: selinexor with bortezomib and dexamethasone, TEAE: treatment-emergent adverse event; TRAE: treatment-related adverse event Vd: bortezomib and dexamethasone.

[a] All SVd population includes 195 patients from the BOSTON SVd arm + 64 patients from the BOSTON crossover arm (SVdX), including 1 additional patient who crossed over from Vd arm since the primary analysis + 42 patients from the supportive study, STOMP.

[b] Based on maximum severity grade of each patient.

[c] The number of patients with dose modification(s) was not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.

[d] Study treatment was selinexor with bortezomib and dexamethasone for SVd arm, and bortezomib with dexamethasone for Vd arm.

Table 22: Most Common Treatment-Emergent Neurological Toxicity Adverse Events, Safety Population – Primary Analysis

MedDRA Preferred Term	SVd Arm (N = 195) n (%)	Vd Arm (N = 204) n (%)	Total (N = 399) n (%)
Patients with At Least One Treatment-Emergent Neurological Toxicity CMQ Adverse Event	**48 (24.6)**	**16 (7.8)**	**64 (16.0)**
Dizziness	24 (12.3)	9 (4.4)	33 (8.3)
Confusional state	16 (8.2)	2 (1.0)	18 (4.5)
Syncope	7 (3.6)	3 (1.5)	10 (2.5)
Amnesia	6 (3.1)	1 (0.5)	7 (1.8)
Cognitive disorder	3 (1.5)	3 (1.5)	6 (1.5)
Somnolence	4 (2.1)	1 (0.5)	5 (1.3)
Delirium	2 (1.0)	1 (0.5)	3 (0.8)
Depressed level of consciousness	0	1 (0.5)	1 (0.3)
Encephalopathy	1 (0.5)	0	1 (0.3)
Hypersomnia	1 (0.5)	0	1 (0.3)

Hepatic events

Table 23: Summary of Hepatobiliary Disorders, Safety Population – Updated Analysis

Patients with at Least One	All SVd (N = 301) n (%)	BOSTON SVd Arm (N = 195) n (%)	BOSTON Vd Arm (N = 204) n (%)
Treatment-Emergent Adverse Event	28 (9.3)	24 (12.3)	18 (8.8)
Grade 3/4 TEAE [1]	9 (3.0)	7 (3.6)	9 (4.4)
Grade 4 TEAE [1]	1 (0.3)	1 (0.5)	0
Serious TEAE	1 (0.3)	1 (0.5)	1 (0.5)
TEAE Leading to Dose Modification in Any Study Treatment [2] [3]	9 (3.0)	8 (4.1)	5 (2.5)
TEAE Leading to Dose Reduction in Any Study Treatment	3 (1.0)	3 (1.5)	1 (0.5)
TEAE Leading to Dose Interruption in Any Study Treatment	7 (2.3)	6 (3.1)	5 (2.5)
TEAE Leading to Study Treatment Discontinuation	1 (0.3)	1 (0.5)	0
TEAE Leading to Death	0	0	0
Treatment-Emergent Treatment-Related Adverse Event [4]	19 (6.3)	16 (8.2)	7 (3.4)
Grade 3/4 TRAE [1]	6 (2.0)	5 (2.6)	2 (1.0)
Grade 4 TRAE [1]	1 (0.3)	1 (0.5)	0
Serious TRAE	0	0	0
TRAE Leading to Dose Modification in Any Study Treatment [2] [3]	8 (2.7)	7 (3.6)	3 (1.5)
TRAE Leading to Dose Reduction in Any Study Treatment	3 (1.0)	3 (1.5)	1 (0.5)
TRAE Leading to Dose Interruption in Any Study Treatment	6 (2.0)	5 (2.6)	3 (1.5)
TRAE Leading to Study Treatment Discontinuation	0	0	0
TRAE Leading to Death	0	0	0

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[1] Based on maximum severity grade of each patient.

[2] The number of patients with dose modification(s) is not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.

[3] Study treatment is selinexor with bortezomib and dexamethasone for SVd Arm, and bortezomib with dexamethasone for Vd Arm.

[4] An AE is considered treatment-related if it is selinexor-related and/or bortezomib-related and/or dexamethasone-related.

Cardiac toxicity

A CMQ of cardiac toxicity retrieved PTs of tachycardia, atrial fibrillation, sinus tachycardia and supraventricular extrasystoles.

Table 24: Summary of Cardiac Toxicity, Safety Population – Updated Analysis

Patients With At Least 1	All SVd (N=301[a]) n (%)	BOSTON SVd Arm (N=195) n (%)	BOSTON Vd Arm (N=204) n (%)
Treatment-emergent adverse event	23 (7.6)	21 (10.8)	7 (3.4)
Grade 3/4 TEAE[b]	4 (1.3)	3 (1.5)	1 (0.5)
Grade 4 TEAEb[b]	0	0	0
Treatment-emergent SAE	5 (1.7)	5 (2.6)	2 (1.0)
TEAE leading to dose modification in any study treatment[c,d]	7 (2.3)	7 (3.6)	2 (1.0)
TEAE leading to dose reduction in any study treatment	1 (0.3)	1 (0.5)	0
TEAE leading to dose interruption in any study treatment	7 (2.3)	7 (3.6)	2 (1.0)
TEAE leading to study treatment discontinuation	1 (0.3)	1 (0.5)	0
TEAE leading to death	0	0	0

Source: Table 14.3.2.1.1.15_updated.
Data cut-off date: 15 Feb 2021 (BOSTON); 01 Sep 2019 (STOMP)
SAE: adverse event; SVd: selinexor with bortezomib and dexamethasone, TEAE: treatment-emergent adverse event; TRAE: treatment-related adverse event Vd: bortezomib and dexamethasone.
[a] All SVd population includes 195 patients from the BOSTON SVd arm + 64 patients from the BOSTON crossover arm (SVdX), including 1 additional patient who crossed over from Vd arm since the primary analysis + 42 patients from the supportive study, STOMP.
[b] Based on maximum severity grade of each patient.
[c] The number of patients with dose modification(s) was not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.
[d] Study treatment was selinexor with bortezomib and dexamethasone for SVd arm, and bortezomib with dexamethasone for Vd arm.

Laboratory findings

Haematology

Table 30: Summary of grade shift in haematology by treatment group, Safety Population – Updated analysis

	SVd Arm (N = 195) n (%)	Vd Arm (N = 204) n (%)	Total (N = 399) n (%)
Hemoglobin increased			
Evaluable Patients [1]	195	201	396
Shift to Any Grade	0	0	0
Shift from Grade <3 to Grade 3 or 4	0	0	0
Shift from Grade <3 to Grade 3	0	0	0
Shift from Grade <3 to Grade 4	0	0	0
Anemia			
Evaluable Patients [1]	195	201	396
Shift to Any Grade	141 (72.3)	103 (51.2)	244 (61.6)
Shift from Grade <3 to Grade 3 or 4	34 (17.4)	24 (11.9)	58 (14.6)
Shift from Grade <3 to Grade 3	34 (17.4)	24 (11.9)	58 (14.6)
Shift from Grade <3 to Grade 4	0	0	0
Leukocytosis			
Evaluable Patients [1]	195	201	396

	SVd Arm (N = 195) n (%)	Vd Arm (N = 204) n (%)	Total (N = 399) n (%)
Shift to Any Grade	0	0	0
Shift from Grade <3 to Grade 3 or 4	0	0	0
Shift from Grade <3 to Grade 3	0	0	0
Shift from Grade <3 to Grade 4	0	0	0
Leukopenia			
Evaluable Patients [1]	195	201	396
Shift to Any Grade	130 (66.7)	67 (33.3)	197 (49.7)
Shift from Grade <3 to Grade 3 or 4	20 (10.3)	5 (2.5)	25 (6.3)
Shift from Grade <3 to Grade 3	18 (9.2)	4 (2.0)	22 (5.6)
Shift from Grade <3 to Grade 4	2 (1.0)	1 (0.5)	3 (0.8)
Lymphocytosis			
Evaluable Patients [1]	188	195	383
Shift to Any Grade	2 (1.1)	9 (4.6)	11 (2.9)
Shift from Grade <3 to Grade 3 or 4	0	0	0
Shift from Grade <3 to Grade 3	0	0	0
Shift from Grade <3 to Grade 4	0	0	0
Lymphocytopenia			
Evaluable Patients [1]	188	195	383
Shift to Any Grade	147 (78.2)	137 (70.3)	284 (74.2)
Shift from Grade <3 to Grade 3 or 4	76 (40.4)	49 (25.1)	125 (32.6)
Shift from Grade <3 to Grade 3	62 (33.0)	41 (21.0)	103 (26.9)
Shift from Grade <3 to Grade 4	14 (7.4)	8 (4.1)	22 (5.7)
Neutropenia			
Evaluable Patients [1]	188	195	383
Shift to Any Grade	92 (48.9)	38 (19.5)	130 (33.9)
Shift from Grade <3 to Grade 3 or 4	22 (11.7)	13 (6.7)	35 (9.1)
Shift from Grade <3 to Grade 3	18 (9.6)	8 (4.1)	26 (6.8)
Shift from Grade <3 to Grade 4	4 (2.1)	5 (2.6)	9 (2.3)
Thrombocytopenia			
Evaluable Patients [1]	195	201	396
Shift to Any Grade	181 (92.8)	103 (51.2)	284 (71.7)
Shift from Grade <3 to Grade 3 or 4	86 (44.1)	40 (19.9)	126 (31.8)
Shift from Grade <3 to Grade 3	59 (30.3)	24 (11.9)	83 (21.0)
Shift from Grade <3 to Grade 4	27 (13.8)	16 (8.0)	43 (10.9)

Clinical chemistry

Table 25: Grade Shifts in Clinical Chemistry Laboratory Parameters from Baseline to Worst On-study Postbaseline Value, Safety Population – Updated analysis

	SVd Arm (N = 195) n (%)	Vd Arm (N = 204) n (%)	Total (N = 399) n (%)
Alanine Aminotransferase (ALT) increased			
Evaluable Patients [1]	195	201	396
Shift to Any Grade	65 (33.3)	60 (29.9)	125 (31.6)
Shift from Grade <3 to Grade 3 or 4	7 (3.6)	1 (0.5)	8 (2.0)
Shift from Grade <3 to Grade 3	6 (3.1)	1 (0.5)	7 (1.8)
Shift from Grade <3 to Grade 4	1 (0.5)	0	1 (0.3)
Hypoalbuminemia			
Evaluable Patients [1]	194	200	394
Shift to Any Grade	54 (27.8)	71 (35.5)	125 (31.7)
Shift from Grade <3 to Grade 3 or 4	1 (0.5)	1 (0.5)	2 (0.5)
Shift from Grade <3 to Grade 3	1 (0.5)	1 (0.5)	2 (0.5)
Shift from Grade <3 to Grade 4	0	0	0
Alkaline Phosphatase (ALP) increased			
Evaluable Patients [1]	195	201	396
Shift to Any Grade	25 (12.8)	34 (16.9)	59 (14.9)
Shift from Grade <3 to Grade 3 or 4	0	1 (0.5)	1 (0.3)
Shift from Grade <3 to Grade 3	0	1 (0.5)	1 (0.3)
Shift from Grade <3 to Grade 4	0	0	0
Aspartate Aminotransferase (AST) increased			
Evaluable Patients [1]	194	201	395
Shift to Any Grade	48 (24.7)	40 (19.9)	88 (22.3)
Shift from Grade <3 to Grade 3 or 4	4 (2.1)	1 (0.5)	5 (1.3)
Shift from Grade <3 to Grade 3	4 (2.1)	1 (0.5)	5 (1.3)
Shift from Grade <3 to Grade 4	0	0	0
Hyperbilirubinaemia			
Evaluable Patients [1]	195	201	396
Shift to Any Grade	33 (16.9)	27 (13.4)	60 (15.2)
Shift from Grade <3 to Grade 3 or 4	2 (1.0)	4 (2.0)	6 (1.5)
Shift from Grade <3 to Grade 3	2 (1.0)	4 (2.0)	6 (1.5)
Shift from Grade <3 to Grade 4	0	0	0

	SVd Arm (N = 195) n (%)	Vd Arm (N = 204) n (%)	Total (N = 399) n (%)
Hypercalcemia			
Evaluable Patients [1]	195	200	395
Shift to Any Grade	18 (9.2)	21 (10.5)	39 (9.9)
Shift from Grade <3 to Grade 3 or 4	3 (1.5)	0	3 (0.8)
Shift from Grade <3 to Grade 3	2 (1.0)	0	2 (0.5)
Shift from Grade <3 to Grade 4	1 (0.5)	0	1 (0.3)
Hypocalcemia			
Evaluable Patients [1]	195	200	395
Shift to Any Grade	108 (55.4)	95 (47.5)	203 (51.4)
Shift from Grade <3 to Grade 3 or 4	4 (2.1)	2 (1.0)	6 (1.5)
Shift from Grade <3 to Grade 3	2 (1.0)	0	2 (0.5)
Shift from Grade <3 to Grade 4	2 (1.0)	2 (1.0)	4 (1.0)
Blood Urea Nitrogen increased			
Evaluable Patients [1]	84	88	172
Shift to Any Grade	33 (39.3)	35 (39.8)	68 (39.5)
Shift from Grade <3 to Grade 3 or 4	4 (4.8)	3 (3.4)	7 (4.1)
Shift from Grade <3 to Grade 3	3 (3.6)	3 (3.4)	6 (3.5)
Shift from Grade <3 to Grade 4	1 (1.2)	0	1 (0.6)
Creatine Kinase increased			
Evaluable Patients [1]	170	172	342
Shift to Any Grade	19 (11.2)	16 (9.3)	35 (10.2)
Shift from Grade <3 to Grade 3 or 4	0	1 (0.6)	1 (0.3)
Shift from Grade <3 to Grade 3	0	1 (0.6)	1 (0.3)
Shift from Grade <3 to Grade 4	0	0	0
Creatinine increased			
Evaluable Patients [1]	195	201	396
Shift to Any Grade	56 (28.7)	50 (24.9)	106 (26.8)
Shift from Grade <3 to Grade 3 or 4	7 (3.6)	3 (1.5)	10 (2.5)
Shift from Grade <3 to Grade 3	7 (3.6)	2 (1.0)	9 (2.3)
Shift from Grade <3 to Grade 4	0	1 (0.5)	1 (0.3)
Hyperglycemia			
Evaluable Patients [1]	104	103	207
Shift to Any Grade	66 (63.5)	46 (44.7)	112 (54.1)
Shift from Grade <3 to Grade 3 or 4	3 (2.9)	3 (2.9)	6 (2.9)
Shift from Grade <3 to Grade 3	3 (2.9)	3 (2.9)	6 (2.9)

	SVd Arm (N = 195) n (%)	Vd Arm (N = 204) n (%)	Total (N = 399) n (%)
Shift from Grade <3 to Grade 4	0	0	0
Hypoglycemia			
Evaluable Patients [1]	104	103	207
Shift to Any Grade	8 (7.7)	18 (17.5)	26 (12.6)
Shift from Grade <3 to Grade 3 or 4	2 (1.9)	0	2 (1.0)
Shift from Grade <3 to Grade 3	1 (1.0)	0	1 (0.5)
Shift from Grade <3 to Grade 4	1 (1.0)	0	1 (0.5)
Hypermagnesemia			
Evaluable Patients [1]	190	195	385
Shift to Any Grade	14 (7.4)	23 (11.8)	37 (9.6)
Shift from Grade <3 to Grade 3 or 4	1 (0.5)	2 (1.0)	3 (0.8)
Shift from Grade <3 to Grade 3	1 (0.5)	2 (1.0)	3 (0.8)
Shift from Grade <3 to Grade 4	0	0	0
Hypomagnesemia			
Evaluable Patients [1]	190	195	385
Shift to Any Grade	50 (26.3)	47 (24.1)	97 (25.2)
Shift from Grade <3 to Grade 3 or 4	1 (0.5)	2 (1.0)	3 (0.8)
Shift from Grade <3 to Grade 3	1 (0.5)	2 (1.0)	3 (0.8)
Shift from Grade <3 to Grade 4	0	0	0
Hypophosphatemia			
Evaluable Patients [1]	192	192	384
Shift to Any Grade	119 (62.0)	83 (43.2)	202 (52.6)
Shift from Grade <3 to Grade 3 or 4	47 (24.5)	19 (9.9)	66 (17.2)
Shift from Grade <3 to Grade 3	45 (23.4)	19 (9.9)	64 (16.7)
Shift from Grade <3 to Grade 4	2 (1.0)	0	2 (0.5)
Hyperkalemia			
Evaluable Patients [1]	195	201	396
Shift to Any Grade	37 (19.0)	43 (21.4)	80 (20.2)
Shift from Grade <3 to Grade 3 or 4	8 (4.1)	5 (2.5)	13 (3.3)
Shift from Grade <3 to Grade 3	6 (3.1)	5 (2.5)	11 (2.8)
Shift from Grade <3 to Grade 4	2 (1.0)	0	2 (0.5)
Hypokalemia			
Evaluable Patients [1]	195	201	396
Shift to Any Grade	55 (28.2)	47 (23.4)	102 (25.8)
Shift from Grade <3 to Grade 3 or 4	13 (6.7)	7 (3.5)	20 (5.1)

	SVd Arm (N = 195) n (%)	Vd Arm (N = 204) n (%)	Total (N = 399) n (%)
Shift from Grade <3 to Grade 3	11 (5.6)	7 (3.5)	18 (4.5)
Shift from Grade <3 to Grade 4	2 (1.0)	0	2 (0.5)
Hypernatremia			
Evaluable Patients [1]	195	201	396
Shift to Any Grade	13 (6.7)	20 (10.0)	33 (8.3)
Shift from Grade <3 to Grade 3 or 4	0	0	0
Shift from Grade <3 to Grade 3	0	0	0
Shift from Grade <3 to Grade 4	0	0	0
Hyponatremia			
Evaluable Patients [1]	195	201	396
Shift to Any Grade	115 (59.0)	50 (24.9)	165 (41.7)
Shift from Grade <3 to Grade 3 or 4	27 (13.8)	6 (3.0)	33 (8.3)
Shift from Grade <3 to Grade 3	26 (13.3)	6 (3.0)	32 (8.1)
Shift from Grade <3 to Grade 4	1 (0.5)	0	1 (0.3)

Source: Table 14.3.4.1.2.2 -updated
[1] Patients with non-missing measurement at baseline and at least one post-baseline measurement.
Note: For patients who cross over, measurements collected after crossover are not included.
Note: The percentage will be based on the number of evaluable patients for each test.

ECG

In the BOSTON study ECG assessments were performed at baseline on all patients and at end of treatment or as clinically indicated. A total of 148 patients (37.1%) had baseline ECGs that were abnormal but not clinically significant (70 [35.9%] in the SVd arm and 78 [38.2%] in the Vd arm). Three patients (0.8% of total) had baseline ECG results that were abnormal but clinically significant, all in the Vd arm.

Table 2: Electrocardiogram: Summary of Overall Interpretation (Safety Analysis Population) – Updated analysis

	SVd Arm (N = 195) n (%)	Vd Arm (N = 204) n (%)	Total (N = 399) n (%)
Overall Interpretation			
Baseline			
Normal	124 (63.6)	122 (59.8)	246 (61.7)
Abnormal, not clinically significant	70 (35.9)	78 (38.2)	148 (37.1)
Abnormal, clinically significant	0	3 (1.5)	3 (0.8)
Missing	1 (0.5)	1 (0.5)	2 (0.5)
Patients with Any Post-Baseline ECG	88 (45.1)	75 (36.8)	163 (40.9)
Worst On-Study Post-Baseline Result [1]			
Normal	51 (58.0)	43 (57.3)	94 (57.7)
Abnormal, not clinically significant	27 (30.7)	30 (40.0)	57 (35.0)
Abnormal, clinically significant	10 (11.4)	2 (2.7)	12 (7.4)
Missing	0	0	0

Table 26: Summary of Shift in Electrocardiogram QTcF (Safety Population) – Updated analysis

		Baseline QTcF (ms)				
Arm	**ECG - QTcF (ms)**	**<430 (Male) or <450 (Female) n (%)**	**430 - 450 (Male) or 450 - 470 (Female) n (%)**	**>450 (Male) or >470 (Female) n (%)**	**Missing n (%)**	**Total n (%)**
SVd	Patients with Any Post-Baseline Measurement	78	3	4	2	87
	Highest On-Study Post-Baseline Measurement [1]					
	>450 (Male) or >470 (Female)	9 (11.5)	0	1 (25.0)	0	10 (11.5)
	>=500	2 (2.6)	0	0	0	2 (2.3)
	Increase from Baseline >10	31 (39.7)	0	0	0	31 (35.6)
	Increase from Baseline >30	16 (20.5)	0	0	0	16 (18.4)
	Increase from Baseline >60	7 (9.0)	0	0	0	7 (8.0)
	Last On-Study Post-Baseline Measurement [1]					
	>450 (Male) or >470 (Female)	7 (9.0)	0	0	0	7 (8.0)
	>=500	1 (1.3)	0	0	0	1 (1.1)
	Increase from Baseline >10	29 (37.2)	0	0	0	29 (33.3)
	Increase from Baseline >30	14 (17.9)	0	0	0	14 (16.1)
	Increase from Baseline >60	5 (6.4)	0	0	0	5 (5.7)

		Baseline QTcF (ms)				
Arm	**ECG - QTcF (ms)**	**<430 (Male) or <450 (Female) n (%)**	**430 - 450 (Male) or 450 - 470 (Female) n (%)**	**>450 (Male) or >470 (Female) n (%)**	**Missing n (%)**	**Total n (%)**
Vd	Patients with Any Post-Baseline Measurement	58	11	1	0	70
	Highest On-Study Post-Baseline Measurement [1]					
	>450 (Male) or >470 (Female)	0	4 (36.4)	1 (100.0)	0	5 (7.1)
	>=500	0	0	0	0	0
	Increase from Baseline >10	26 (44.8)	1 (9.1)	0	0	27 (38.6)
	Increase from Baseline >30	10 (17.2)	0	0	0	10 (14.3)
	Increase from Baseline >60	1 (1.7)	0	0	0	1 (1.4)
	Last On-Study Post-Baseline Measurement [1]					
	>450 (Male) or >470 (Female)	0	4 (36.4)	1 (100.0)	0	5 (7.1)
	>=500	0	0	0	0	0
	Increase from Baseline >10	24 (41.4)	1 (9.1)	0	0	25 (35.7)
	Increase from Baseline >30	10 (17.2)	0	0	0	10 (14.3)
	Increase from Baseline >60	1 (1.7)	0	0	0	1 (1.4)

Safety in special populations

Age

Table 34: Summary of Adverse Events - Subgroup Analysis by Age Group (<75 vs. ≥75) Treatment-Emergent Adverse Events By Treatment Arm - All Patients in the Safety Population

	SVd Arm			Vd Arm		
Patients with at Least One	**Age <75 (N = 161) n (%)**	**Age >=75 (N = 34) n (%)**	**Total (N = 195) n (%)**	**Age <75 (N = 159) n (%)**	**Age >=75 (N = 45) n (%)**	**Total (N = 204) n (%)**
Treatment-Emergent Adverse Event	161 (100.0)	33 (97.1)	194 (99.5)	154 (96.9)	44 (97.8)	198 (97.1)
Grade 3/4 TEAE [1]	124 (77.0)	29 (85.3)	153 (78.5)	91 (57.2)	24 (53.3)	115 (56.4)
Grade 4 TEAE [1]	34 (21.1)	3 (8.8)	37 (19.0)	19 (11.9)	3 (6.7)	22 (10.8)
Serious TEAE	89 (55.3)	17 (50.0)	106 (54.4)	58 (36.5)	21 (46.7)	79 (38.7)
TEAE Leading to Dose Modification in Any Study Treatment [2] [3]	142 (88.2)	31 (91.2)	173 (88.7)	121 (76.1)	35 (77.8)	156 (76.5)
TEAE Leading to Dose Reduction in Any Study Treatment	116 (72.0)	25 (73.5)	141 (72.3)	83 (52.2)	23 (51.1)	106 (52.0)
TEAE Leading to Dose Interruption in Any Study Treatment	137 (85.1)	30 (88.2)	167 (85.6)	107 (67.3)	32 (71.1)	139 (68.1)
TEAE Leading to Study Treatment Discontinuation	31 (19.3)	10 (29.4)	41 (21.0)	23 (14.5)	11 (24.4)	34 (16.7)
TEAE Leading to Death	14 (8.7)	0	14 (7.2)	6 (3.8)	7 (15.6)	13 (6.4)
Treatment-Emergent Treatment-Related Adverse Event [4]	155 (96.3)	32 (94.1)	187 (95.9)	131 (82.4)	36 (80.0)	167 (81.9)
Grade 3/4 TRAE [1]	112 (69.6)	25 (73.5)	137 (70.3)	65 (40.9)	19 (42.2)	84 (41.2)
Grade 4 TRAE [1]	25 (15.5)	3 (8.8)	28 (14.4)	15 (9.4)	2 (4.4)	17 (8.3)
Serious TRAE	47 (29.2)	11 (32.4)	58 (29.7)	20 (12.6)	4 (8.9)	24 (11.8)
TRAE Leading to Dose Modification in Any Study Treatment [2] [3]	130 (80.7)	28 (82.4)	158 (81.0)	102 (64.2)	29 (64.4)	131 (64.2)
TRAE Leading to Dose Reduction in Any Study Treatment	115 (71.4)	24 (70.6)	139 (71.3)	81 (50.9)	21 (46.7)	102 (50.0)
TRAE Leading to Dose Interruption in Any Study Treatment	118 (73.3)	27 (79.4)	145 (74.4)	74 (46.5)	23 (51.1)	97 (47.5)
TRAE Leading to Study Treatment Discontinuation	25 (15.5)	7 (20.6)	32 (16.4)	18 (11.3)	9 (20.0)	27 (13.2)
TRAE Leading to Death	4 (2.5)	0	4 (2.1)	1 (0.6)	0	1 (0.5)

Source: Table 14.3.1.1.13.1.2- updated
Note: For patients who cross over, AEs that occurred after the crossover are not included.
[1] Based on maximum severity grade of each patient.

Sex

Table 35: Summary of Adverse Events - Subgroup Analysis by Sex Treatment-Emergent Adverse Events By Treatment Arm - All Patients in the Safety Population

	SVd Arm			Vd Arm		
Patients with at Least One	**Male (N = 115) n (%)**	**Female (N = 80) n (%)**	**Total (N = 195) n (%)**	**Male (N = 113) n (%)**	**Female (N = 91) n (%)**	**Total (N = 204) n (%)**
Treatment-Emergent Adverse Event	114 (99.1)	80 (100.0)	194 (99.5)	111 (98.2)	87 (95.6)	198 (97.1)
Grade 3/4 TEAE [1]	91 (79.1)	62 (77.5)	153 (78.5)	62 (54.9)	53 (58.2)	115 (56.4)
Grade 4 TEAE [1]	18 (15.7)	19 (23.8)	37 (19.0)	13 (11.5)	9 (9.9)	22 (10.8)
Serious TEAE	55 (47.8)	51 (63.8)	106 (54.4)	43 (38.1)	36 (39.6)	79 (38.7)
TEAE Leading to Dose Modification in Any Study Treatment [2] [3]	100 (87.0)	73 (91.3)	173 (88.7)	89 (78.8)	67 (73.6)	156 (76.5)
TEAE Leading to Dose Reduction in Any Study Treatment	78 (67.8)	63 (78.8)	141 (72.3)	60 (53.1)	46 (50.5)	106 (52.0)
TEAE Leading to Dose Interruption in Any Study Treatment	94 (81.7)	73 (91.3)	167 (85.6)	78 (69.0)	61 (67.0)	139 (68.1)
TEAE Leading to Study Treatment Discontinuation	20 (17.4)	21 (26.3)	41 (21.0)	20 (17.7)	14 (15.4)	34 (16.7)
TEAE Leading to Death	7 (6.1)	7 (8.8)	14 (7.2)	6 (5.3)	7 (7.7)	13 (6.4)
Treatment-Emergent Treatment-Related Adverse Event [4]	109 (94.8)	78 (97.5)	187 (95.9)	92 (81.4)	75 (82.4)	167 (81.9)
Grade 3/4 TRAE [1]	78 (67.8)	59 (73.8)	137 (70.3)	47 (41.6)	37 (40.7)	84 (41.2)
Grade 4 TRAE [1]	13 (11.3)	15 (18.8)	28 (14.4)	11 (9.7)	6 (6.6)	17 (8.3)
Serious TRAE	30 (26.1)	28 (35.0)	58 (29.7)	14 (12.4)	10 (11.0)	24 (11.8)
TRAE Leading to Dose Modification in Any Study Treatment [2] [3]	90 (78.3)	68 (85.0)	158 (81.0)	76 (67.3)	55 (60.4)	131 (64.2)

Patients with at Least One	Male (N = 115) n (%)	Female (N = 80) n (%)	Total (N = 195) n (%)	Male (N = 113) n (%)	Female (N = 91) n (%)	Total (N = 204) n (%)
TRAE Leading to Dose Reduction in Any Study Treatment	78 (67.8)	61 (76.3)	139 (71.3)	60 (53.1)	42 (46.2)	102 (50.0)
TRAE Leading to Dose Interruption in Any Study Treatment	79 (68.7)	66 (82.5)	145 (74.4)	58 (51.3)	39 (42.9)	97 (47.5)
TRAE Leading to Study Treatment Discontinuation	15 (13.0)	17 (21.3)	32 (16.4)	18 (15.9)	9 (9.9)	27 (13.2)
TRAE Leading to Death	2 (1.7)	2 (2.5)	4 (2.1)	0	1 (1.1)	1 (0.5)

Source: Table 14.3.1.1.13.1.3-updated
Note: For patients who cross over, AEs that occurred after the crossover are not included.
[1] Based on maximum severity grade of each patient.
[2] The number of patients with dose modification(s) is not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.
[3] Study treatment is selinexor with bortezomib and dexamethasone for SVd Arm. Study treatment is bortezomib with dexamethasone for Vd Arm.
[4] For patients in SVd Arm, an AE is considered treatment-related if it is selinexor-related and/or bortezomib-related and/or dexamethasone-related. For patients in Vd Arm, an AE is considered treatment-related if it is bortezomib-related and/or dexamethasone-related.

Race

Table 36: Summary of Adverse Events - Subgroup Analysis by Race Treatment-Emergent Adverse Events By Treatment Arm All Patients in the Safety Population

	SVd Arm			Vd Arm		
Patients with at Least One	White (N = 161) n (%)	Races other than White (N = 34) n (%)	Total (N = 195) n (%)	White (N = 162) n (%)	Races other than White (N = 42) n (%)	Total (N = 204) n (%)
Treatment-Emergent Adverse Event	160 (99.4)	34 (100.0)	194 (99.5)	156 (96.3)	42 (100.0)	198 (97.1)
Grade 3/4 TEAE [1]	128 (79.5)	25 (73.5)	153 (78.5)	90 (55.6)	25 (59.5)	115 (56.4)
Grade 4 TEAE [1]	33 (20.5)	4 (11.8)	37 (19.0)	19 (11.7)	3 (7.1)	22 (10.8)
Serious TEAE	83 (51.6)	23 (67.6)	106 (54.4)	64 (39.5)	15 (35.7)	79 (38.7)
TEAE Leading to Dose Modification in Any Study Treatment [2] [3]	143 (88.8)	30 (88.2)	173 (88.7)	118 (72.8)	38 (90.5)	156 (76.5)
TEAE Leading to Dose Reduction in Any Study Treatment	115 (71.4)	26 (76.5)	141 (72.3)	78 (48.1)	28 (66.7)	106 (52.0)
TEAE Leading to Dose Interruption in Any Study Treatment	139 (86.3)	28 (82.4)	167 (85.6)	107 (66.0)	32 (76.2)	139 (68.1)

TEAE Leading to Study Treatment Discontinuation	35 (21.7)	6 (17.6)	41 (21.0)	25 (15.4)	9 (21.4)	34 (16.7)
TEAE Leading to Death	10 (6.2)	4 (11.8)	14 (7.2)	11 (6.8)	2 (4.8)	13 (6.4)
Treatment-Emergent Treatment-Related Adverse Event [4]	153 (95.0)	34 (100.0)	187 (95.9)	127 (78.4)	40 (95.2)	167 (81.9)
Grade 3/4 TRAE [1]	116 (72.0)	21 (61.8)	137 (70.3)	68 (42.0)	16 (38.1)	84 (41.2)
Grade 4 TRAE [1]	25 (15.5)	3 (8.8)	28 (14.4)	15 (9.3)	2 (4.8)	17 (8.3)
Serious TRAE	39 (24.2)	19 (55.9)	58 (29.7)	21 (13.0)	3 (7.1)	24 (11.8)
TRAE Leading to Dose Modification in Any Study Treatment [2] [3]	130 (80.7)	28 (82.4)	158 (81.0)	98 (60.5)	33 (78.6)	131 (64.2)
TRAE Leading to Dose Reduction in Any Study Treatment	113 (70.2)	26 (76.5)	139 (71.3)	75 (46.3)	27 (64.3)	102 (50.0)
TRAE Leading to Dose Interruption in Any Study Treatment	121 (75.2)	24 (70.6)	145 (74.4)	76 (46.9)	21 (50.0)	97 (47.5)
TRAE Leading to Study Treatment Discontinuation	27 (16.8)	5 (14.7)	32 (16.4)	20 (12.3)	7 (16.7)	27 (13.2)
TRAE Leading to Death	2 (1.2)	2 (5.9)	4 (2.1)	1 (0.6)	0	1 (0.5)

Source: Table 14.3.1.1.13.1.4-updated
Note: For patients who cross over, AEs that occurred after the crossover are not included.
[1] Based on maximum severity grade of each patient.
[2] The number of patients with dose modification(s) is not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.
[3] Study treatment is selinexor with bortezomib and dexamethasone for SVd Arm. Study treatment is bortezomib with dexamethasone for Vd Arm.
[4] For patients in SVd Arm, an AE is considered treatment-related if it is selinexor-related and/or bortezomib-related and/or dexamethasone-related. For patients in Vd Arm, an AE is considered treatment-related if it is bortezomib-related and/or dexamethasone-related.

Renal impairment

Table 37: Summary of Adverse Events - Subgroup Analysis by Baseline Creatinine Clearance Treatment-Emergent Adverse Events By Treatment Arm - All Patients in the Safety Population

	SVd Arm				Vd Arm			
Patients with at Least One	**Creatinine Clearance <30 mL/min (N = 3) n (%)**	**Creatinine Clearance 30-60 mL/min (N = 53) n (%)**	**Creatinine Clearance >60 mL/min (N = 139) n (%)**	**Total (N = 195) n (%)**	**Creatinine Clearance <30 mL/min (N = 9) n (%)**	**Creatinine Clearance 30-60 mL/min (N = 58) n (%)**	**Creatinine Clearance >60 mL/min (N = 137) n (%)**	**Total (N = 204) n (%)**
Treatment-Emergent Adverse Event	3 (100.0)	53 (100.0)	138 (99.3)	194 (99.5)	8 (88.9)	57 (98.3)	133 (97.1)	198 (97.1)
Grade 3/4 TEAE [1]	2 (66.7)	41 (77.4)	110 (79.1)	153 (78.5)	4 (44.4)	33 (56.9)	78 (56.9)	115 (56.4)
Grade 4 TEAE [1]	0	11 (20.8)	26 (18.7)	37 (19.0)	0	7 (12.1)	15 (10.9)	22 (10.8)
Serious TEAE	3 (100.0)	28 (52.8)	75 (54.0)	106 (54.4)	5 (55.6)	26 (44.8)	48 (35.0)	79 (38.7)
TEAE Leading to Dose Modification in Any Study Treatment [2] [3]	3 (100.0)	48 (90.6)	122 (87.8)	173 (88.7)	6 (66.7)	48 (82.8)	102 (74.5)	156 (76.5)
TEAE Leading to Dose Reduction in Any Study Treatment	3 (100.0)	35 (66.0)	103 (74.1)	141 (72.3)	4 (44.4)	30 (51.7)	72 (52.6)	106 (52.0)
TEAE Leading to Dose Interruption in Any Study Treatment	3 (100.0)	47 (88.7)	117 (84.2)	167 (85.6)	6 (66.7)	43 (74.1)	90 (65.7)	139 (68.1)
TEAE Leading to Study Treatment Discontinuation	0	11 (20.8)	30 (21.6)	41 (21.0)	1 (11.1)	13 (22.4)	20 (14.6)	34 (16.7)
TEAE Leading to Death	1 (33.3)	2 (3.8)	11 (7.9)	14 (7.2)	2 (22.2)	6 (10.3)	5 (3.6)	13 (6.4)
Treatment-Emergent Treatment-Related Adverse Event [4]	3 (100.0)	49 (92.5)	135 (97.1)	187 (95.9)	6 (66.7)	48 (82.8)	113 (82.5)	167 (81.9)
Grade 3/4 TRAE [1]	3 (100.0)	35 (66.0)	99 (71.2)	137 (70.3)	3 (33.3)	28 (48.3)	53 (38.7)	84 (41.2)
Grade 4 TRAE [1]	0	8 (15.1)	20 (14.4)	28 (14.4)	0	5 (8.6)	12 (8.8)	17 (8.3)
Serious TRAE	2 (66.7)	20 (37.7)	36 (25.9)	58 (29.7)	2 (22.2)	6 (10.3)	16 (11.7)	24 (11.8)

TRAE Leading to Dose Modification in Any Study Treatment [2] [3]	3 (100.0)	41 (77.4)	114 (82.0)	158 (81.0)	5 (55.6)	38 (65.5)	88 (64.2)	131 (64.2)
TRAE Leading to Dose Reduction in Any Study Treatment	3 (100.0)	34 (64.2)	102 (73.4)	139 (71.3)	4 (44.4)	28 (48.3)	70 (51.1)	102 (50.0)
TRAE Leading to Dose Interruption in Any Study Treatment	3 (100.0)	40 (75.5)	102 (73.4)	145 (74.4)	3 (33.3)	31 (53.4)	63 (46.0)	97 (47.5)
TRAE Leading to Study Treatment Discontinuation	0	7 (13.2)	25 (18.0)	32 (16.4)	1 (11.1)	11 (19.0)	15 (10.9)	27 (13.2)
TRAE Leading to Death	0	1 (1.9)	3 (2.2)	4 (2.1)	0	0	1 (0.7)	1 (0.5)

Source: Table 14.3.1.1.13.1.5- updated
Note: For patients who cross over, AEs that occurred after the crossover are not included.
[1] Based on maximum severity grade of each patient.
[2] The number of patients with dose modification(s) is not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.
[3] Study treatment is selinexor with bortezomib and dexamethasone for SVd Arm. Study treatment is bortezomib with dexamethasone for Vd Arm.
[4] For patients in SVd Arm, an AE is considered treatment-related if it is selinexor-related and/or bortezomib-related and/or dexamethasone-related. For patients in Vd Arm, an AE is considered treatment-related if it is bortezomib-related and/or dexamethasone-related.

Hepatic impairment

Table: Summary of TEAEs by Baseline Hepatic Function and Treatment Arm (All Patients in the Safety Population)

Patients with at Least One	SVd Arm(N=195)		Vd Arm (N=204)	
	Normal Hepatic Function (N=167) n (%)	Mild Hepatic Impairment (N=25)[a] n (%)	Normal Hepatic Function (N=188) n (%)	Mild/ Moderate Hepatic Impairment (N=16) n (%)[b]
TEAE	166 (99.4)	25 (100.0)	183 (97.3)	15 (93.8)
Grade 3/4 TEAE[c]	129 (77.2)	21 (84.0)	107 (56.9)	8 (50.0)
Grade 4 TEAE[c]	32 (19.2)	5 (20.0)	21 (11.2)	1 (6.3)
SAE	87 (52.1)	18 (72.0)	72 (38.3)	7 (43.8)
TEAE Leading to Dose Modification in Any Study Treatment[d]	148 (88.6)	24 (96.0)	142 (75.5)	14 (87.5)
TEAE Leading to Dose Reduction	122 (73.1)	18 (72.0)	96 (51.1)	10 (62.5)
TEAE Leading to Dose Interruption	142 (85.0)	24 (96.0)	127 (67.6)	12 (75.0)
TEAE Leading to Study Treatment Discontinuation	36 (21.6)	5 (20.0)	31 (16.5)	3 (18.8)
TEAE Leading to Death	11 (6.6)	3 (12.0)	12 (6.4)	1 (6.3)

SAE = serious adverse event; SVd=selinexor plus bortezomib plus low-dose dexamethasone; TEAE = treatment-emergent adverse event; Vd=bortezomib plus low-dose dexamethasone.
Source: Table 14.4.3.2.1, Table 14.4.3.2.4
Data cut-off date: 15 Feb 2021.
a There were no patients with moderate or severe hepatic impairment in the SVd arm and 3 patients had missing baseline hepatic function assessment in the SVd arm.
b Of the 16 patients with mild/moderate hepatic impairment in the Vd arm, 12 patients had mild hepatic impairment and 4 patients had moderate hepatic impairment. No patient had severe hepatic impairment.
c Based on maximum severity grade of each patient.
d The number of patients with dose modification(s) is not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.

Safety related to drug-drug interactions and other interactions

See PK/PD section

Discontinuation due to adverse events

As of the updated analysis, TEAEs leading to discontinuation of study treatment were reported in 67 (22.3%) patients in the All SVd population and 41 (21.0%) patients in the BOSTON SVd arm compared with 34 (16.7%) patients in the BOSTON Vd arm (Table 29). No additional patients discontinued study treatment due to TEAEs in the BOSTON SVd arm since the primary analysis. Of the total 34 patients in the BOSTON Vd arm who discontinued treatment due to TEAEs, 2 discontinued (1 due to PN and 1 due to corona virus infection) after the primary analysis.

PN remained the most common cause of treatment discontinuation across all 3 groups, with a higher incidence in the BOSTON Vd arm (7.8%) compared with the All SVd (4.0%) and BOSTON SVd arm (4.6%).

Table 38: Treatment-Emergent Adverse Events Leading to Study Treatment Discontinuation Occurring in ≥1% of Patients in the All SVd Population, Safety Population – Updated Analysis

MedDRA System Organ Class MedDRA Preferred Term	All SVd (N=301[a]) n (%)	BOSTON SVd Arm (N=195) n (%)	BOSTON Vd Arm (N=204) n (%)
Patients with at least 1 TEAE leading to treatment discontinuation	67 (22.3)	41 (21.0)	34 (16.7)
Blood and lymphatic system disorders	9 (3.0)	5 (2.6)	1 (0.5)
Thrombocytopenia	8 (2.7)	4 (2.1)	1 (0.5)
Anaemia	4 (1.3)	2 (1.0)	0
Gastrointestinal disorders	12 (4.0)	9 (4.6)	3 (1.5)
Nausea	9 (3.0)	6 (3.1)	0
Vomiting	4 (1.3)	4 (2.1)	0
General disorders and administration site conditions	18 (6.0)	13 (6.7)	3 (1.5)
Fatigue	10 (3.3)	7 (3.6)	1 (0.5)
Infections and infestations	4 (1.3)	2 (1.0)	5 (2.5)
Pneumonia	3 (1.0)	1 (0.5)	0
Investigations	5 (1.7)	3 (1.5)	1 (0.5)
Weight decreased	3 (1.0)	2 (1.0)	1 (0.5)
Metabolism and nutrition disorders	9 (3.0)	6 (3.1)	2 (1.0)
Decreased appetite	6 (2.0)	4 (2.1)	1 (0.5)
Nervous system disorders	21 (7.0)	12 (6.2)	20 (9.8)
Neuropathy peripheral	12 (4.0)	9 (4.6)	16 (7.8)
Cognitive disorder	4 (1.3)	1 (0.5)	2 (1.0)
Psychiatric disorders	12 (4.0)	6 (3.1)	1 (0.5)
Confusional state	3 (1.0)	2 (1.0)	0
Depression	3 (1.0)	0	0

Source: Table 14.3.1.7.1.1_updated and 14.3.1.7.1.2_updated.
Data cut-off date: 15 Feb 2021 (BOSTON); 01 Sep 2019 (STOMP)
Note: This table uses MedDRA version 22.0. System Organ Classes were recoded to aggregate medically similar SOCs. Preferred Terms were recoded to aggregate medically similar PTs.
MedDRA: Medical Dictionary for Regulatory Activities; SVd: selinexor with bortezomib and dexamethasone; TEAE: treatment-emergent adverse event; Vd: bortezomib and dexamethasone.
[a] All SVd population includes 195 patients from the BOSTON SVd arm + 64 patients from the BOSTON crossover arm (SVdX), including 1 additional patient who crossed over from the Vd arm since the primary analysis + 42 patients from the supportive study, STOMP.

Adverse events leading to dose reduction

Overall, 253 (63.4%) patients in the Safety Population experienced dose reduction due to any cause. The frequency dose reduction was higher in the SVd arm compared with the Vd arm (73.3% versus 53.9%, respectively).

Table 39: Treatment-Emergent Adverse Events Leading to Dose Reduction in ≥4 Patients in Either Arm (Safety Population) – Updated analysis

MedDRA Preferred Term	SVd Arm (N = 195) n (%)	Vd Arm (N = 204) n (%)	Total (N = 399) n (%)
Neuropathy peripheral	39 (20.0)	58 (28.4)	97 (24.3)
Thrombocytopenia	65 (33.3)	9 (4.4)	74 (18.5)
Fatigue	21 (10.8)	5 (2.5)	26 (6.5)
Asthenia	14 (7.2)	5 (2.5)	19 (4.8)
Insomnia	10 (5.1)	8 (3.9)	18 (4.5)
Weight decreased	14 (7.2)	4 (2.0)	18 (4.5)
Decreased appetite	17 (8.7)	0	17 (4.3)
Nausea	14 (7.2)	0	14 (3.5)
Diarrhoea	4 (2.1)	7 (3.4)	11 (2.8)
Oedema peripheral	5 (2.6)	5 (2.5)	10 (2.5)
Neutropenia	8 (4.1)	0	8 (2.0)
Dyspnoea	4 (2.1)	3 (1.5)	7 (1.8)
Vomiting	6 (3.1)	1 (0.5)	7 (1.8)
Cataract	5 (2.6)	1 (0.5)	6 (1.5)
Pneumonia	5 (2.6)	1 (0.5)	6 (1.5)
Anaemia	5 (2.6)	0	5 (1.3)
Confusional state	5 (2.6)	0	5 (1.3)
Hyperglycaemia	4 (2.1)	1 (0.5)	5 (1.3)

Source: Table14.4.3.4.4
Note: For patients who cross over, AEs that occur after the crossover are not included.
Note: This table uses MedDRA version 22.0. Preferred Terms are recorded to aggregate medically similar PTs.

In the updated analysis, TEAEs leading to dose reduction were reported in 141 (72.3%) patients in the SVd arm and 106 (52.0%) patients in the Vd arm. No additional patients required dose reduction due to TEAEs in the SVd arm since the primary analysis. Of the 106 patients with dose reductions due to TEAEs in the Vd arm, 2 patients had at least 1 TEAE leading to dose reduction after the primary analysis.

The proportion of patients with dose reductions due to TEAEs was higher in the SVd arm compared with the Vd arm (72.3% versus 52.0%). The most common AEs leading to dose reduction were PN (SVd, 20.0%; Vd, 28.4%), thrombocytopenia (SVd, 33.3%; Vd, 4.4%), and fatigue (SVd, 10.8%; Vd, 2.5%).

Adverse events leading to dose interruption

Overall, 328 (82.2%) patients in the Safety Population experienced dose delay or interruption due to any cause. The frequency of dose delay or interruption was higher in the SVd arm compared with the Vd arm (88.7% versus 76.0%, respectively).

The most frequently reported TEAEs leading to dose interruption in patients receiving SVd were thrombocytopenia (34.9%), asthenia (13.8%), fatigue (13.8%) and pneumonia (10.8%) In patients

receiving Vd, the most frequently reported were PN (18.1%), pneumonia (10.8%), upper respiratory tract infection (9.8%), asthenia (7.8%), and thrombocytopenia (7.8%).

Table 40: Treatment-emergent Adverse Events Leading to Dose Interruption in ≥4 Patients in Either Arm (Safety Population) – Updated analysis

MedDRA Preferred Term	SVd Arm (N = 195) n (%)	Vd Arm (N = 204) n (%)	Total (N = 399) n (%)
Thrombocytopenia	69 (35.4)	16 (7.8)	85 (21.3)
Neuropathy peripheral	16 (8.2)	37 (18.1)	53 (13.3)
Pneumonia	22 (11.3)	23 (11.3)	45 (11.3)
Asthenia	28 (14.4)	16 (7.8)	44 (11.0)
Upper respiratory tract infection	24 (12.3)	20 (9.8)	44 (11.0)
Fatigue	28 (14.4)	4 (2.0)	32 (8.0)
Pyrexia	16 (8.2)	14 (6.9)	30 (7.5)
Bronchitis	15 (7.7)	14 (6.9)	29 (7.3)
Diarrhoea	15 (7.7)	12 (5.9)	27 (6.8)
Decreased appetite	18 (9.2)	2 (1.0)	20 (5.0)
Neutropenia	17 (8.7)	2 (1.0)	19 (4.8)
Cough	11 (5.6)	7 (3.4)	18 (4.5)
Anaemia	12 (6.2)	5 (2.5)	17 (4.3)
Lower respiratory tract infection	9 (4.6)	8 (3.9)	17 (4.3)
Dyspnoea	6 (3.1)	8 (3.9)	14 (3.5)
Influenza	10 (5.1)	4 (2.0)	14 (3.5)
Nausea	14 (7.2)	0	14 (3.5)
Weight decreased	12 (6.2)	2 (1.0)	14 (3.5)
Urinary tract infection	7 (3.6)	2 (1.0)	9 (2.3)
Cataract	8 (4.1)	0	8 (2.0)
Infection	5 (2.6)	3 (1.5)	8 (2.0)
Herpes zoster	3 (1.5)	4 (2.0)	7 (1.8)
Oedema peripheral	2 (1.0)	5 (2.5)	7 (1.8)
Vomiting	6 (3.1)	0	6 (1.5)
Acute kidney injury	5 (2.6)	0	5 (1.3)
C-reactive protein increased	1 (0.5)	4 (2.0)	5 (1.3)
Confusional state	5 (2.6)	0	5 (1.3)
Oropharyngeal pain	4 (2.1)	1 (0.5)	5 (1.3)
Epistaxis	4 (2.1)	0	4 (1.0)
Gastroenteritis	4 (2.1)	0	4 (1.0)
Insomnia	0	4 (2.0)	4 (1.0)
Overdose	4 (2.1)	0	4 (1.0)

Source: Table 14.4.3.4.5
Note: For patients who cross over, AEs that occur after the crossover are not included.
Note: This table uses MedDRA version 22.0. Preferred Terms are recorded to aggregate medically similar PTs.

In the updated analysis, the proportion of patients with dose delay or interruption due to at least 1 TEAE remained unchanged from the primary analysis and was higher in the SVd arm compared with the Vd arm (85.6% versus 68.1%).

2.5.1. Post marketing experience

As of 15 Feb 2021, approximately 2659 patients were treated with XPOVIO (selinexor). Adverse event reports (n=1397) from the commercial use of selinexor have been received through 15 Feb 2021 and are in line with the expected side effect profile based on the package insert for RRMM. Majority of the events were non-serious (84.2%) and 15.8% events were serious. There have been 222 fatal reports among the approximately 2659 patients who received selinexor since its commercial availability. According to the MAH, the postmarketing safety data with selinexor is consistent with what was observed during the clinical studies and no new safety signals were identified.

Table 27: Commercial use of XPOVIO through 15 February 2021

	Total
Approximate Number of Patients	2659
Number of Reports	1397 Cases
Expedited Cases	1074 Submissions
Fatal Reports	222
Number of Events; n	7367
Nonserious Events; n (%)	6203 (84.2%)
Serious Events; n (%)	1164 (15.8%)

Source: Patient exposure calculated using actual sales and patient experience collected from Karyopharm Safety Database

Table 28: Adverse events from postmarketing experience

Preferred Term	N
Nausea	670
Fatigue	512
Decreased appetite	485
Diarrhoea	353
Vomiting	274
Thrombocytopenia	274
Weight decreased	229
Asthenia	214
Anaemia	201
Death	195
Plasma cell myeloma	178
Constipation	131
Dizziness	120
Dehydration	117
Confusional state	84
Leukopenia	73
Hyponatraemia	70
Dyspnoea	69
Fall	63
Drug ineffective	61

Source: Karyopharm Safety Database

2.5.2. Discussion on clinical safety

Through the current variation application, the MAH is seeking an extension of the indication for selinexor in combination with bortezomib and dexamethasone for the treatment of adult patients with RRMM who had received 1 to 3 prior regimens.

Safety data of this application is mainly based on results from the **BOSTON study** (KCP-330-023), a Phase 3 randomised, open-label, multicenter study in which selinexor in combination with bortezomib and dexamethasone (SVd; **n=195**) was compared with bortezomib plus dexamethasone (Vd; n=204). In addition, safety data of 42 patients included in Arm 2 of the study STOMP (KCP-330-017) have been provided which is considered supportive, since not all of these patients received the recommended dosing regimen for SVd. Pooled safety data of the BOSTON and STOMP studies as well as data of the 64 patients who crossed over from the Vd arm to the SVd arm in the BOSTON study have been submitted (n=301).

Safety data discussed below are based on the last data cut-off (**15 Feb 2021**) from the BOSTON study.

In the BOSTON study selinexor was administered at a dose of 100 mg PO plus bortezomib 1.3 mg/m2 SC plus dexamethasone 40 mg (20 mg dose 2 days per week) in 35-days cycles. It should be noted that the recommended dose of selinexor in combination with bortezomib and dexamethasone differs from the one currently authorised (i.e. 80 mg on days 1 and 3 in combination with dexamethasone). As per protocol, a selinexor dose escalation (i.e. increase selinexor to a fixed 60 mg dose BIW during Weeks 1 through 5 of each cycle and dexamethasone 20 mg BIW on the same days as selinexor) may be considered for patients who do not achieve at least a PR within the first 2 cycles, were tolerating SVd and do not have any AEs related to study treatment Grade >2 at the time of dose escalation.

At the time of the data cut-off 37 (9.3%) patients were still on treatment (21 in the SVd arm and 16 in the Vd arm). Disease progression was the main cause for treatment discontinuation in both treatment arms (76 [39%] patient SVd and 118 [57.8%] patients Vd). A higher number of patients in the SVd arm withdrawn consent compared with Vd (37 [19.0%] vs. 21 [10.3%], respectively). The main reasons for patient withdrawal consent were related to AEs, logistical reasons and poor health/entered hospice care. Further, even though numbers are low, double of the patients discontinued treatment in the SVd arm due to physician decision (10 [5.1%] vs. 5 [2.5%]), being the main reason "patient not benefitting from treatment/PD not approved by IRC" (3 patients in each treatment arm). Other causes in the SVd arm included adverse events, poor health and logistical reasons. Somehow, these data reflect the increased toxicity of the combination with the addition of selinexor.

Median treatment duration was similar between treatment arms (30 weeks in the SVd arm and 32 weeks in the Vd arm), with a treatment exposure of at least 48 weeks (i.e. around 11 months) in 35.9% and 32.4% of patients, respectively. Dose modifications were more frequent in the SVd group compared with the Vd group (91.8% vs. 82.4%). As previously observed in the STORM study (i.e. in RRMM patients), dose delay/interruption (86.7%) and dose reduction (65.6%) to selinexor were frequent. It is important to note that doses of bortezomib and dexamethasone were lower in the experimental arm than in the control arm. However, dose delay/interruption to bortezomib (82.1% vs. 74.0%) and dexamethasone (80.0% vs. 72.5%) were higher in the SVd arm. According to the MAH, the higher rate of dose delay/interruptions to bortezomib and dexamethasone may be due to concomitant discontinuation of selinexor, since in most cases the three drugs were interrupted or delayed for most TEAEs. There were 51 (26.2%) patients with dose escalation in the SVd arm and 17 (8.3%) in the Vd arm. The MAH clarified that the majority of these dose increases were dose readjustments after a preceding dose reduction in selinexor and only 16 patients in the SVd arm had a dose escalation to selinexor 60 mg BIW. Besides, dose escalation in the Vd arm referred to dose increases of either bortezomib or dexamethasone after a previous dose reduction.

Patients included in the study had a median age of 67 (range: 38, 90) years. There were 79 patient who were ≥75 years, with a higher rate in the Vd arm (34 [17.4%] vs. 45 [22.1%]). Most of patients had an ECOG performance status of 0 or 1. There were 20 (10.3%) patients in the SVd arm and 15 (7.4%) in the Vd arm with ECOG 2. All patients had received prior antineoplastic therapy, with a median of 1 and 2 prior lines of anti-MM therapy in the SVd and Vd arms (range: 1, 3), respectively. According to the protocol patients must have received at least 1 prior anti-MM regimen and no more than 3 prior anti-MM regimens. A BSA <1.4 m^2 at baseline was an exclusion criterion and according to the protocol, in no case may the selinexor dose exceed 70 mg/m^2 per dose for any patient. In the SVd arm baseline median BSA was 1.85 (range: 1.4, 2.4). The MAH was requested to clarify what was the recommendation for those patients (if any) that due to body weight fluctuations reached a BSA <1.4 m^2 during the study and justify whether any dose restriction according to BSA should be included in the SmPC. According to the MAH only 2 patients reached a BSA <1.4 m^2 during the study. In both cases, the dose of selinexor had been previously reduced due to toxicity and was lower than the stipulated limit. Bearing in mind that a higher exposure may be translated into higher toxicity and considering the already known safety profile of selinexor a restriction not to exceed the 70 mg/m^2 per dose has been included in the SmPC.

Most patients (99.5%) received at least 1 concomitant medication. In the SVd arm, most commonly treatments received were antiemetics, mainly serotonin (5-HT_3) antagonists (88.2%).

Patients with symptomatic ischemia, uncontrolled clinically significant conduction abnormalities, congestive heart failure of New York Heart Association Class ≥3 or known left ventricular ejection fraction <40%, or myocardial infarction within 3 months prior to C1D1 were excluded from the study.

Almost all patients reported at least one adverse event (>97%) in both treatment arms. The **most commonly reported** adverse events (AEs) (≥20%) in the SVd arm were thrombocytopenia (62.1% SVd vs. 27.5% Vd), nausea (50.3% vs. 10.3%), fatigue (42.1% vs. 18.1%), anaemia (37.4% vs. 23.5%), decreased appetite (35.4% vs. 5.4%), diarrhoea (33.3% vs. 25.5%), peripheral neuropathy (33.3% vs. 48.5%), weight decreased (26.2% vs. 12.3%), vomiting (20.5% vs. 4.9%), cataract (23.6% vs. 7.4%) and asthenia (25.1% vs. 13.2%).

There were other less frequent AEs with a higher incidence in the SVd arm compared with the Vd arm, such as visual impairment (7.2% vs. 2.0%), upper respiratory tract infection (20.5% vs. 14.7%), nasopharyngitis (11.8% vs. 4.9%), septic shock (2.1% vs. 0), hyponatraemia (7.7% vs. 1.5%), hypophosphatemia (8.7% vs. 3.4%), dizziness (12.3% vs. 4.4%), dysgeusia (6.7% vs. 0.5%), confusional state (8.2% vs. 1.0%), depression (3.6% vs. 0) and oropharyngeal pain (7.2% vs. 2%). Cardiac AEs were also more frequent in the SVd arm (17.4% vs. 7.8%), although it does not appear to be driven by any particular PT.

A higher proportion of patients reported TEAEs of haemorrhage in the SVd arm compared with the Vd arm (34 [17.4%] vs. 15 (7.4%)]), although most of these events were of grade 1 or 2. The most common TEAEs of haemorrhage in the SVd arm were epistaxis (5.6%) and contusion (3.1%). The incidence of TEAEs of Grade 3-4 and Grade 5 were comparable between treatment arms. However, SAEs were more frequent in the SVd arm (7 [3.6%] vs. 1 [0.5%]) and there were 8 (4.1%) patients that discontinued treatment due to a TEAE (while none in the control arm). SAEs included two fatal TEAEs (1 cerebral haemorrhage and 1 haemorrhagic shock). The event of cerebral haemorrhage occurred after only one dose of selinexor and in the context of PD; thus it appears unlikely to be related to selinexor treatment. However, contribution of selinexor to the haemorrhagic shock fatal TEAE cannot be ruled out, since it occurred in a patient with thrombocytopenia, which is a known ADR of selinexor. Other SAEs were epistaxis (3), haematuria (1) and lower gastrointestinal haemorrhage. The events of epistaxis occurred in patients with thrombocytopenia, which is a known ADR of selinexor, therefore, they can be considered related to selinexor (even if in some of them other confounding factors were also present). Moreover, in one of these patients an event of melena was also reported. Regarding the events of lower

gastrointestinal haemorrhage and haematuria, a causal relationship with selinexor cannot be established. Information on the risk of thrombocytopenia as well as significant bleeding in patients treated with selinexor is already included in the SmPC.

There were 10 (5.1%) patients in the SVd arm with an event of overdose (7 were due to selinexor overdose). Five of these patients had a TEAE. In most of the cases of selinexor overdose the patient had took an extra dose of selinexor. There was also one patient that erroneously took 320 mg of selinexor who suffer a SAE of pulmonary embolism that resolved. No other SAEs were reported. Medication errors is included as an important potential risk in the RMP.

AEs of **Grade 3/4** were more frequently reported in the SVd arm compared with the Vd arm (78.5% vs. 56.4%). The most frequently reported (≥10%) in the SVd arm were thrombocytopenia (40.5% vs. 17.6%), anaemia (16.4% vs. 9.8%), fatigue (13.3% vs. 1%) and cataract (11.3% vs. 2%).

Of note, the indicende of Grade ≥2 peripheral neuropathy events was a secondary endpoint in the BOSTON study. A lower rate of Grade ≥ 2 peripheral neuropathy events was reported in the SVd arm compared with the Vd arm (42 [21.5%] vs. 73 [35.8%] Vd), which is not unexpected taking into account the lower dose of bortezomib in the experimental arm.

Up to the data cut-off, 147 patients had died in the BOSTON study (68 [34.9%] SVd and 79 [38.7%] Vd). According to the MAH most of these **deaths** were due to disease progression (33/68 [48.5%]) SVd and 35/80 [43.8%] Vd). There were 34 patients who died while on treatment or withing 30 days of the last dose of study treatment (16 [8.2%] and 18 [8.8%] patients in the SVd and Vd groups, respectively), the majority of these deaths were related to an AE (13 [6.7%] and 14 [6.9%]). In the SVd arm the most common AEs leading to death were pneumonia (3 [1.5%] SVd vs. 4 [2.0%] Vd) and septic shock (3 [1.5%] vs 0). According to the MAH, the 3 fatal AEs of septic shock occurred in India (see further comments below). Moreover, there were 10 deaths due to AEs reported in patients who crossed over from the Vd arm to SVdX (9 events) and SdX (1 event). Of the 9 AEs leading to death in the SVdX arm, 4 patients died within 30 days of the last dose of Vd and within 7 days of SVdX treatment.

Serious adverse events (**SAEs**) were more frequent in the SVd arm compared with the Vd arm (54.4% vs. 38.7%). In the SVd arm more than a half of these SAEs were considered treatment related (29.7% vs. 11.8%). The most commonly reported SAEs (regardless of causality) were pneumonia (14.9% SVd vs. 13.2% Vd), cataract (4.6% vs. 0) and sepsis (4.1% vs. 1.0%).

There were 41 (21%) patients in the SVd arm and 34 (16.7%) in the Vd arm that required **treatment discontinuation** due to AEs. The main AEs leading to discontinuation was peripheral neuropathy (9 [4.6%] SVd vs. 16 [7.8%] Vd) which is related to bortezomib treatment. Other AEs that led to treatment discontinuation in the SVd arm were fatigue (7 [3.6%]), nausea (6 [3.1%]), thrombocytopenia, vomiting and decreased appetite (2.1% each), all of them considered ADRs of selinexor.

Dose modifications due to AEs were also frequent. In the SVd arm 72.3% of patients required any dose reduction compared with 52% of patients in the Vd arm. The main AEs that led to dose reductions in the SVd arm were thrombocytopenia (33.3% SVd vs. 4.4% Vd), peripheral neuropathy (20% vs. 28.4%) and fatigue (10.8% vs. 2.5%). Further, 85.6% in the SVd arm and 68.1% in the Vd required dose interruption during the study. The main AEs that led to dose interruption in the Sd arm were thrombocytopenia (35.4%), asthenia (14.4%), fatigue (14.4%), upper respiratory tract infection (12.3%), and pneumonia (11.3%).

Adverse events of special interest (AESIs)

According to the protocol of the BOSTON study, AESIs for selinexor include cataracts and acute cerebellar syndrome (ACS). Further, the MAH has provided brief summaries of other significant adverse events, called AEs of clinical interest, which include cytopenias (thrombocytopenia, neutropenia), gastrointestinal

events (nausea, vomiting), decreased appetite/weight decreased, infections (pneumonia, sepsis, opportunistic infections), eye disorders (blurred vision, cataract), hyponatremia, neurological and cardiac toxicity and hepatobiliary disorders. According to the MAH, these AEs were selected based on identified and potential risks of selinexor.

Thrombocytopenia is a known ADR of selinexor. In the BOSTON study 62.1% of patients reported an event of thrombocytopenia, with 40.5% of events of Grade 3/4 and 3 SAEs. No fatal adverse events were reported. According to the MAH events were managed with dose modifications (40% SVd vs. 17.6%), thrombopoietin (TPO) receptor agonists (29.3% SVd vs. 4.5% Vd) and platelet growth factors and platelet transfusions. Among patients with Grade ≥3 AEs of thrombocytopenia bleeding events were reported in 4 (5.1%) patients in the SVd arm and 2 (5.6%) patients in the Vd arm, thus despite the higher rate of thrombocytopenia in the SVd arm, it does not seem to be associated with an increased risk of bleeding events.

Neutropenia was reported in 31 (15.9%) patients in the SVd arm and 14 (6.9%) patients in the Vd arm. The majority of events were of Grade 1 or 2. AEs of Grade 3/4 were reported in 9.7% and 3.9% of patients respectively. Febrile neutropenia was reported in 1 patient in each treatment arm. According to the MAH, neutropenia events were managed with dose modifications ang G-CSF treatment.

Gastrointestinal adverse events, including vomiting and nausea, are among the most frequently reported AEs in patients treated with selinexor. Other characteristic AEs of selinexor are decreased appetite and weight decreased. As previously discussed at the time of the MAA, these AEs (including fatigue) have been reported with other XPO-1 inhibitors and are considered a class effect. While the exact mechanism associated to these AEs is unknown, it is considered they might be mediated by CNS toxicity. According to the MAH in most cases several of these AEs were concurrent. Although it is acknowledged that most of these events were mild, they led to treatment discontinuation in several patients despite treatment measures. As per protocol, all patients should receive 5-HT3 antagonists (or alternative treatment if the patient does not tolerate 5-HT3 antagonists), starting on C1D1 before the first dose of study treatment. It is important to implement early measures (i.e. dose modifications and supportive treatments) in patients treated with selinexor, particularly taking into account the inherent risk of these patients to suffer from this type of AEs.

In the BOSTON study 8 (4.1%) patients reported AEs of sepsis in the SVd arm compared with 2 (1.0%). According to the MAH, disbalances between treatment arms are mainly driven by 4 cases reported in India, of which 3 were fatal, in 23 patients treated with SVd. The MAH argues that the higher rate of sepsis in India may be due to an inadequate management of these patients, in addition to prior treatments received and the presence of other conditions such as asthma. Further, the MAH states that 2 of these 4 patients had significant weight loss, an important identified risk of selinexor. According to the MAH, additional measures were implemented and since then no new cases were identified and even SAEs were reduced. Safety data from the 23 patients treated with SVd in India have been provided. SAEs were more frequent in patients from India compared with other countries (65.2% vs. 50%), mainly vomiting (3 [13%] vs. 4 [2.3%]) and septic shock (3 [13%] vs. 1 [0.6%]). Treatment discontinuation was also more frequent in patients from India (17.4% vs. 4.7).

The incidence of opportunistic infections was almost double in the SVd arm compared with Vd arm (8.2% vs. 4.4%), although SAEs were similar (3 [1.5%] vs. 2 [1%]) and no fatal AEs were reported. The most frequent opportunistic infections were candida infections, herpes zoster, herpes virus and to a lesser extent respiratory syncytial virus infection. SAEs of opportunistic infections reported in the SVd arm were respiratory syncytial virus (2 events) and meningitis tuberculous (1 event).

Blurred vision and cataract, respectively, are considered very common and common ADRs of selinexor. In the BOSTON study 27 (13.8%) patients reported AE of blurred vision, most of them mild/moderate

and no SAEs were observed. Regarding cataract, a higher rate of AEs of cataract was reported in the SVd arm compared with the Vd arm (23.6% vs. 7.4%). Of these, 11 (11.3%) were of Grade 3/4 in the SVd arm while only 4 (2.0%) in the Vd arm. Further, there were 9 (4.6%) patients with SAEs in the SVd and none in the Vd arm. According to the MAH, the higher risk of cataract in the SVd arm vs Vd arm may be related to selinexor increasing the risk of glucocorticoid-associated cataract. Ophthalmology examination (OE) during screening was performed in approximately 97% of patients. Of these, 120 (61.5%) in the SVd and 130 (63.7%) in the Vd had cataract at baseline. A warning regarding cataract has been included in section 4.4. of the SmPC.

Neurological toxicity was reported in 48 (24.6%) patients in the SVd arm while 16 (7.8%) in the Vd arm. Of these, 8 (4.1%) and 3 (1.5%) patients, reported AEs of Grade 3 and SAEs in the SVd group, respectively. The most frequently reported AEs were dizziness and confusional state, which are already included as ADRs in the SmPC. Considering the All SVd population (i.e. including patients who crossed over from the Vd to the SVd arm and patients from STOMP study), a total of 6 patients reported neurological SAEs, including 2 delirium, 2 syncope, 1 encephalopathy and 1 cognitive disorder/confusional state and most of them were considered related to selinexor treatment by the investigator.

A higher incidence of cardiac events was reported in the SVd arm compared with the Vd arm (10.8% vs 3.4%). There were 3 (1.5%) vs. 1 (0.5%) AEs of Grade 3 and 5 (2.6%) vs 2 (1.0%) SAEs, in the SVd and Vd groups, respectively. No fatal AEs were reported. Tachycardia and atrial fibrillation were the most commonly reported. In fact, most of SAEs were atrial fibrillation. Tachycardia is currently included as ADR of selinexor. Regarding atrial fibrillation the incidence was slightly higher in the SVd arm (7 [3.6%] vs. 3 [1.5%]) and at least in 4 patients the event was considered serious. However, in many of these cases, other risk factors were present and therefore a clear relationship with selinexor cannot be established at this stage. The MAH is encouraged to closely monitor it through routine pharmacovigilance activities.

No events of tumour lysis syndrome (TLS) were reported in the SVd arm of the BOSTON study. TLS is included as an ADR in the SmPC (sections 4.4. and 4.8). According to the MAH, there were no cases of ACS in the BOSTON study (neither in the STOMP study).

Laboratory findings

Overall, laboratory findings are reflecting the safety profile of selinexor. Shifts to a worst post-baseline value (i.e. from Grade<3 to Grade 3 or 4) observed in clinical parameters in a higher rate in the SVd arm compared with the Vd arm were leukopenia (10.3% vs. 2.5%), lymphocytopenia (38.3% vs. 25.1%), thrombocytopenia (42.6% vs. 19.4%), hypophosphatemia (23.4% vs. 9.9%) and hyponatremia (13.8% vs 3.0%).

ECG assessments were performed at baseline on all patients and at end of treatment or as clinically indicated. Of the 72 and 52 patients in the SVd and Vd arm, respectively, with any post-baseline ECG, in the SVd group there were 2 (2.8%) patients with a QTcF≥500 and 7 (9.7%) with an increase from baseline >60 while no QTcF values ≥500 were reported in the Vd arm and only 1 (1.9%) patient had an increase >60. According to the MAH, most of these patients had history of cardiac events and no cases of Torsade de Pointes nor any other ventricular arrhythmia were reported.

Subgroups of special interest

Safety data have been presented according to age, sex, race and renal function.

With regards to age, a higher rate of SAEs (56.0% vs. 46.5% vs.) and discontinuations (27.5% vs. 12.8%) due to AEs is observed in the subgroup of elderly patients (≥65 years) compared with younger patients (<65). In the subgroup of patients ≥75 years (n=34) the incidence of Grade 3/4 AEs was

increased. However, a similar pattern is also observed in the control arm. By PT, fatigue, dizziness and confusional state were more frequent in elderly patients. It is however surprising that cataract, whose incidence increase with age, was more frequent in patients <65 (15.6% vs. 29.1%). According to the MAH a definitive mechanism for the imbalance in the cataract rates could not be identified and it is considered that several factors may have contributed (i.e. longer duration of exposure to study treatment in younger patients, a higher median number of prior lines received, a higher total dexamethasone dose received and a higher median duration of the most recent prior therapy).

The safety profile of SVd appears to be worse in female patients, according to the higher rates of Grade 4 AEs (21.3% female vs. 14.8% male), SAEs (61.3% vs. 45.2%), dose reductions (78.8% vs. 67.8%), dose interruptions (91.3% vs. 81.7%) and study treatment discontinuations (26.3% vs. 17.4%). AEs more frequently reported in women than men were nausea, fatigue, diarrhoea, weigh decreased, vomiting, upper respiratory tract infection, neutropenia, oedema peripheral and hypokalaemia. According to the MAH, the higher incidence of some TEAEs in female patients compared with male patient may be due to the (expected) lower body weight and therefore higher selinexor exposure in female patients. Overall, TEAEs reported in a higher frequency in female patients are already known ADRs of selinexor.

A total of 25 patients in the SVd arm had mild hepatic impairment while none of them had moderate hepatic impairment. Acknowledging the limited sample size, a higher rate of TEAEs of Grade 3/4, SAEs, dose interruptions (all patients except one required a dose interruption) and deaths were reported in patients with mild hepatic impairment treated with SVd compared with patients with normal hepatic function. However, the number of patients with mild hepatic impairment was low and differences do not appear to be driven by any particular TEAE.

Additional expert consultations

NA

Assessment of paediatric data on clinical safety

NA

2.5.3. Conclusions on clinical safety

The addition of selinexor to Vd involves an increase in toxicity, with higher rates of Grade 3/4 AEs, SAEs, dose modifications and treatment discontinuations.

The most commonly reported AEs (SVd vs Vd) were thrombocytopenia (62.1% vs. 27.5%), nausea (50.3% vs. 10.3%), fatigue (42.1% vs. 18.1%), anaemia (37.4% vs. 23.5%), decreased appetite (35.4% vs. 5.4%), diarrhoea (33.3% vs. 25.5%), peripheral neuropathy (33.3% vs. 48.5%), weight decreased (26.2% vs. 12.3%), vomiting (20.5% vs. 4.9%), cataract (23.6% vs. 7.4%) and asthenia (25.1% vs. 13.2%). Most of these AEs are considered ADRs of selinexor, except for peripheral neuropathy, which is a known ADR of bortezomib. Of note, the incidence of peripheral neuropathy was lower in the SVd arm due to the lower dose of bortezomib. Overall, the safety profile of the combination was consistent with the already known safety profile of its components.

2.5.4. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Significance of paediatric studies

Not applicable

3. Risk management plan

The MAH submitted an updated RMP version 2.0, date of final sign off 07 July 2021 with this application. The (main) proposed RMP changes were the following:

Completion of KCP-330-023/ BOSTON study to fulfil the specific obligation. Update in the safety data to reflect the safety information captured during the KCP-330-023 study and update in the exposure data. Proposed additional product indication and dosing regimen.

Part II - Safety Specification

Part II- Module SIII Clinical trial exposure

This section was updated with information of the KCP-330-023 study.

PRAC Rapporteurs assessment comment: The changes to this section are acceptable.

Part II- Module SV post authorisation exposure

This section was updated with the proposed indication and the post authorisation exposure up to 31 Mar 2020.

PRAC Rapporteurs assessment comment: The changes to this section are acceptable.

Part II- Module SVII.2 New safety concerns and reclassification with a submission of an updated RMP

No new safety concers were included within this updated version of the RMP.

Part II- Module SVII.3.1. Presentation of important identified risks and important potential risks

Throughout this section safety data of the Boston study was added.

Part II- Module SVII - Summary of the safety concerns

Summary of safety concerns	
Important identified risks	Thrombocytopenia and Bleeding Severe infections due to Neutropenia Fatigue Decreased appetite Weight decreased Hyponatraemia Confusional state

Important potential risks	Tumor lysis syndrome Acute cerebellar syndrome Medication error
Missing information	Use in patients with severe renal impairment Use in patients with severe hepatic impairment

Part III - Pharmacovigilance plan

The MAH proposed no changes to this section of the RMP. There are no routine pharmacovigilance activities beyond adverse reaction reporting and signal detection. No additional PV activities are ongoing or planned.

PRAC Rapporteurs assessment comment:

As no new safety concerns have been identified, routine pharmacovigilance activities are considered sufficient to monitor the risks of selinexor in the new indication.

Part IV - Plans for post-authorisation efficacy studies

The MAH removed study KCP330 2023 from the pharmacovigilance plan. With this removal there are no remaining plans for post-authorisation efficacy studies.

PRAC Rapporteurs assessment comment:

As study KCP330-2023 has been finalised it is accepted that this study is removed from the PhV plan.

Part V - Risk minimisation measures

This section of the RMP was updated in line with the proposed wordings in the SmPC and routine risk minimisation measures for the new identified risk of cataract were described.

The MAH proposed no additional risk minimisation measures.

PRAC Rapporteurs assessment comment:

As no new safety concerns have been identified, routine risk minimisation measures are considered sufficient to minimise the risks of selinexor in the new indication.

Part VI: Summary of the risk management plan

The summary of the risk management plan was updated in line with the changes outlined above.

PRAC Rapporteurs assessment comment:

This section should be updated according to the comments above.

3.1. Overall conclusion on the RMP

The changes to the RMP are acceptable.

4. Changes to the Product Information

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

4.1.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

5. Benefit-Risk Balance

5.1. Therapeutic Context

Nexpovio (selinexor) received a conditional marketing authorisation (CMA) valid throughout the EU on 26 March 2021, for its use in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

To fulfil the Specific Obligation (SOB) of the initial CMA the MAH was requested to submit the results of the phase 3, KCP-330-023/BOSTON study comparing the efficacy and safety of selinexor plus bortezomib plus low-dose dexamethasone versus bortezomib plus low dose dexamethasone in adult patients with relapsed/refractory multiple myeloma who have received 1 to 3 prior anti-MM regimens. The present application incorporates both the primary analysis of the BOSTON study as well as updated data using a later data cut-off (15 Feb 2021).

With the current application, the MAH is submitting a Grouped Type II /Type IB variation of selinexor (Nexpovio):

- The **Type II variation** is aimed at extending the indication for Nexpovio to be used "*in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy*" and to fulfil the SOB in the context of the initial CMA, as mentioned above.
- The **Type IB variation** relates to the introduction of a new pack size (8 tablets per pack) for added convenience to patients for dose modification in the new intended treatment setting.

5.1.1. Disease or condition

Multiple myeloma (MM) is a clonal plasma cells disorder, that represents approximately a 0.8% of all cancers worldwide (Ferlay 2015). The proliferation of the malignant clonal plasma cells leads to subsequent replacement of normal bone marrow haematopoietic precursors and overproduction of M-proteins with progressive morbidity and eventual mortality.

Characteristic MM hallmarks include osteolytic lesions, anaemia (due to bone marrow dysfunction), increased susceptibility to infections (due to immunosuppression), hypercalcemia, renal insufficiency/failure, and neurological complications (Palumbo 2011).

5.1.2. Available therapies and unmet medical need

Nowadays, different classes of drugs are available for multiple myeloma patients (alkylators, steroids, proteasome inhibitors [PIs], immunomodulatory agents [IMiDs], histone deacetylase inhibitors [HDACIs] and monoclonal antibodies). Among these treatment options, lenalidomide (an IMiD) and bortezomib (a PI) have a prominent role. Both are used as frontline treatment of MM and in combination with other drugs at relapse.

The International Myeloma Working Group (IMWG) recommends treating relapsed MM patients considering patient-specific factors, tumour characteristics and prior therapy (both type of therapy and the response to the therapy; Ludwig 2014). With disease progression, a change in drug classes is recommended.

5.1.3. Main clinical studies

This application is based on the efficacy results from the pivotal ongoing **Phase 3 KCP-330-023 (BOSTON) study** and supported by the **Phase 1b/2 KCP-330-017 (STOMP) study**.

Results presented below are based on the primary analysis (DCO: 18 Feb 2020), unless otherwise specified.

5.2. Favourable effects

- Treatment with selinexor plus bortezomib plus low-dose dexamethasone (SVd) resulted in a statistically significant improvement in **PFS** in the SVd arm (13.93 months) compared with bortezomib plus low-dose dexamethasone (Vd) (9.46 months); HR=0.70 (95% CI: 0.5279, 0.9335) p=0.0075; at a median overall follow-up of 13.17 and 16.53 months for the SVd and Vd arms, respectively. These results were generally consistent across multiple sensitivity analyses and pre-specified subgroups.
- A higher **ORR** was observed for the SVd group (76.4%) compared with the Vd group (62.3%). The estimate of odds ratio was 1.96 with 95% CI (1.26, 3.05); p =0.0012.
- The rate of **≥VGPR** (sCR + CR + VGPR) was higher for the SVd group (44.6%) compared with the Vd group (32.4%); p=0.0082
- Median **OS** was not reached for SVd at a median follow-up of 17.3 months. The probability of survival was higher for the SVd arm throughout the study. The median OS for patients in the Vd arm was 24.97 months (95% CI: 23.49, NE).
- The median **DOR** in patients with confirmed PR or better was of 20.3 (95% CI: 12.55, NE) months in the SVd arm and 12.9 (95% CI: 9.26, 15.77) months in the Vd arm.
- The median **TTNT** in the SVd arm was 16.1 months (95% CI: 13.9, NE) compared to 10.8 months (95% CI: 9.8, 13.4) in the Vd arm.

The results from the **updated analysis** of the BOSTON study (DCO 15 Feb 2021) were overall consistent with the results of the primary analysis.

Further, updated OS data with a median follow-up of 33.61 months in the SVd arm and 33.84 monhts in the Vd arm (DCO 22 March 2022) showed a HR of 0.93 (95% CI: 0.67, 1.27).

5.3. Uncertainties and limitations about favourable effects

Although the control arm in the BOSTON study is an accepted standard of care, the room for improvement of response of a patient previously exposed to bortezomib, alone or in combination in a previous first line, appears limited with the proposed combination and in fact Vd is usually considered as an option in later lines of treatment. In this context, the control arm in the BOSTON study (Vd) could be considered, at present, as a suboptimal treatment option in the intended treatment setting. This said, it is acknowledged that the treatment landscape for MM patients is evolving quickly and demonstration of superiority vs. the proposed control arm should in principle suffice for regulatory approval.

5.4. Unfavourable effects

In the BOSTON study almost all patients, reported at least one adverse event (>97%) in both treatment arms. The most commonly reported adverse events (AEs) (≥20%) in the SVd arm were thrombocytopenia (62.1% SVd vs. 27.5% Vd), nausea (50.3% vs. 10.3%), fatigue (42.1% vs. 18.1%), anaemia (37.4% vs. 23.5%), decreased appetite (35.4% vs. 5.4%), diarrhoea (33.3% vs. 25.5%), peripheral neuropathy (33.3% vs. 48.5%), weight decreased (26.2% vs. 12.3%), vomiting (20.5% vs. 4.9%), cataract (23.6% vs. 7.4%) and asthenia (25.1% vs. 13.2%).

AEs of Grade 3/4 were reported in 78.5% of patients in the SVd arm and 56.4% in the Vd arm. The most frequently reported AEs of Grade 3/4 (≥10%) in the SVd arm were thrombocytopenia (40.5% vs. 17.6%), anaemia (16.4% vs. 9.8%), fatigue (13.3% vs. 1%) and cataract (11.3% vs. 2%).

Up to the data cut-off, 147 patients had died in the BOSTON study (68 [34.9%] SVd and 79 [38.7%] Vd), most of them due to disease progression. There were 34 patients who died while on treatment or withing 30 days of the last dose of study treatment (16 [8.2%] SVd and 18 [8.8%] Vd groups) and the majority of these deaths were related to an AE (13 [6.7%] SVd and 14 [6.9%] Vd). In the SVd arm the most common AEs leading to death were pneumonia (3 [1.5%] SVd vs. 4 [2.0%] Vd) and septic shock (3 [1.5%] vs 0).

Serious adverse events (SAEs) were more frequent in the SVd arm compared with the Vd arm (54.4% vs. 38.7%). In the SVd arm more than a half of these SAEs were considered treatment related (29.7% vs. 11.8%). The most commonly reported SAEs (regardless of causality) were pneumonia (14.9% SVd vs. 13.2% Vd), cataract (4.6% vs. 0) and sepsis (4.1% vs. 1.0%).

There were 41 (21%) patients in the SVd arm and 34 (16.7%) in the Vd arm that required treatment discontinuation due to AEs. The main AEs leading to discontinuation was peripheral neuropathy (9 [4.6%] SVd vs. 16 [7.8%] Vd) which is related to bortezomib treatment. Other AEs that led to treatment discontinuation in the SVd arm were fatigue (7 [3.6%]), nausea (6 [3.1%]), thrombocytopenia, vomiting and decreased appetite (2.1% each).

In the SVd arm 72.3% of patients required any dose reduction compared with 52% of patients in the Vd arm. The main AEs that led to dose reductions in the SVd arm were thrombocytopenia (33.3% SVd vs. 4.4% Vd), peripheral neuropathy (20% vs. 28.4%) and fatigue (10.8% vs. 2.5%). Further, 85.6% in the SVd arm and 68.1% in the Vd required dose interruption during the study. The main AEs that led to dose interruption in the Sd arm were thrombocytopenia (35.4%), asthenia (14.4%), fatigue (14.4%), upper respiratory tract infection (12.3%), and pneumonia (11.3%).

Other AEs reported in patients treated with SVd and which are known ADRs of selinexor or considered significant AEs of selinexor were thrombocytopenia, neutropenia, nausea, vomiting, decreased appetite/weight decreased, infections (pneumonia, sepsis, opportunistic infections), eye disorders (blurred vision, cataract), hyponatremia, neurological and cardiac toxicity and hepatobiliary disorders.

5.5. Uncertainties and limitations about unfavourable effects

There were no uncertainties in the knowledge about the unfavourable effects.

5.6. Effects Table

Effects table for trial KCP-330-023/BOSTON (eudract: 2016-003957-14): selinexor, bortezomib, and dexamethasone (SVd) versus bortezomib and dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma (RRMM) data cut-off date: 18-feb-2020

Effect	Short description	SVd n=195	Vd n=207	Uncertainties / Strength of evidence	References
Favourable effects					
PFS	Progression Free Survival Hazard Ratio (95% CI) One-sided p-value		0.71 (0.54, 0.93) 0.0075		
	Median PFS in months (95% CI)	13.2 (11.7, Not Reached)	9.5 (8.1, 10.8)		
ORR	Overall Response rate n (%) 95% CI One-sided p-value sCR CR VGPR PR	 150 (76.9) (70.4, 82.6) 0.0012 19 (10) 14 (7) 54 (28) 63 (32)	 131 (63.3) (56.3, 69.9) 0.0012 13 (6) 9 (4) 45 (22) 64 (31)		
Unfavourable effects					
		SVd n=195	**Vd n=204**		
Grade 3/4 AEs	AEs of grade 3 or 4 regardless or causality, n (%)	153 (78.5)	115 (56.4)		
SAEs	SAEs regardless of causality, n (%)	106 (54.4)	79 (38.7)		
Discontinuations due to AEs	Discontinuation due to AEs regardless of causality, n(%)	41 (21.0)	34 (16.7)		
Thrombocytopenia	AEs occurring in ≥20% of patients; n (%)	121 (62.1)	56 (27.5)		
Nausea		98 (50.3)	21 (10.3)		
Fatigue		82 (42.1)	37 (18.1)		
Anaemia		73 (37.4)	48 (23.5)		
Decreased appetite		69 (35.4)	11 (5.4)		
Diarrhoea		65 (33.3)	52 (25.5)		
Weight decreased		51 (26.2)	25 (12.3)		
Neuropathy peripheral		65 (33.3)	99 (48.5)		
Vomiting		40 (20.5)	10 (4.9)		
Cataract		46 (23.6)	15 (7.4)		
Asthenia		49 (25.1)	27 (13.2)		
AEs leading to death		14 (7.2)	13 (6.4)		

AEs=Adverse events; HR=hazard ratio; PFS=progression-free survival; IRC=independent review committee; SVd=selinexor plus bortezomib plus low-dose dexamethasone; Vd=bortezomib plus low-dose dexamethasone.
Note: Progression-free survival is calculated from date of randomization until the first date of IRC-confirmed progressive disease per International Myeloma Working Group response criteria, or death due to any cause, whichever occurred first.
a The Investigator reported 1 patient in All SVd and 1 patient in Vd died due to PD and TEAE. To be conservative, the Sponsor counted these as TEAEs leading to death.
Safety data are based on the data cut-off date 15 Feb 2021

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

Treatment with the (once weekly) combination of selinexor with bortezomib and dexamethasone tested in the BOSTON study (SVd) leads to a significant improvement in median PFS compared to the standard (BIW) Vd regimen in the targeted patient population, i.e. adult patients with multiple myeloma who have received at least one prior therapy. This benefit in terms of PFS is supported by several secondary endpoints. Moreover, no evidence of detrimental effects on survival has been observed also considering that cross over to either SVd or Sd was allowed in the trial.

From the safety point of view, the addition of selinexor to Vd treatment involves a remarkable increase in toxicity, with a higher rate of Grade 3/4 AEs, SAEs and treatment discontinuations. The most commonly reported AEs were thrombocytopenia, nausea, fatigue, anaemia, decreased appetite, diarrhoea, peripheral neuropathy, weight decreased, vomiting, cataract and asthenia. Of note, since doses of bortezomib in the SVd arm were lower than in the Vd arm, a lower incidence of peripheral neuropathy was reported in patients treated with SVd.

5.7.2. Balance of benefits and risks

Selinexor in combination with bortezomib and dexamethasone has demonstrated an improvement in PFS compared to the standard (BIW) Vd regimen in the target patient population (i.e. adult patients with MM who have received at least one prior therapy), which is supported by several secondary endpoints. Despite the toxicity of this combination, it is considered that the benefits of the proposed combination outweigh its risks.

5.7.3. Additional considerations on the benefit-risk balance

The results from the pivotal BOSTON study in support of this application were intended to fulfil the Specific Obligation (SOB) in the context of the Conditional Marketing Authorisation (CMA) of Nexpovio (selinexor) which was granted on 26 March 2021. The SOB is now considered fulfilled. The data from the BOSTON study confirms a positive B/R balance for selinexor in the sought indication and constitute a comprehensive data package supporting granting of a marketing authorisation no longer subject to specific obligations.

5.8. Conclusions

The overall benefit/risk balance of selinexor in the claimed indication is positive.

4. Recommendations

Based on the review of the submitted data, this application regarding the following changes:

Variations requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB
B.II.z	B.II.z - Quality change - Finished product - Other variation	Type IB	I, IIIA and IIIB

- Extension of indication for Nexpovio in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy and,
- Addition of a new pack size (8 tablets) to align with the dose modification guidance for the new indication.
  Accordingly, Sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 6.5 of the SmPC are updated to reflect the new indication and the new pack size.
- Fulfilment of the Specific Obligation agreed in the context of the CMA of Nexpovio via the submission of results from the confirmatory Phase 3 study, KCP-330-023, thereby supporting the granting of a marketing authorisation not subject to specific obligations. Annex II is updated to reflect the completion of the Specific Obligation. The Labelling and Package Leaflet are amended accordingly. The RMP (v 2.0) is amended consequently.

☒is recommended for approval.

In addition, the CHMP, having considered the application as set out in the appended assessment report and having reviewed the data submitted by the marketing authorisation holder including the evidence concerning compliance with specific obligations, is of the opinion that the risk-benefit balance of the above mentioned medicinal product remains favourable, that all specific obligations laid down in Annex II have been fulfilled and that comprehensive data supports a favourable benefit-risk balance of the above mentioned medicinal product. Therefore, pursuant to Article 14-a(8) of Regulation (EC) No 726/2004, the CHMP recommends by consensus the granting of a marketing authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 for the above mentioned medicinal product for which the draft Summary of Product Characteristics is set out in Annex I.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I, IIIA and IIIB, Annex A and to the Risk Management Plan are recommended.

In addition, the following obligation has been fulfilled, and therefore it is recommended that it be deleted from the Annex II to the Opinion:

In order to confirm the efficacy and safety of selinexor in combination with dexamethasone in the treatment of multiple myeloma in adult patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy, the MAH should submit the	May 2021

results of the phase 3, KCP-330-023/BOSTON study (data cut off Feb 2021), comparing the efficacy and safety of selinexor plus bortezomib plus low-dose dexamethasone versus bortezomib plus low dose dexamethasone in adult patients with relapsed/refractory multiple myeloma who have received 1 to 3 prior anti-MM regimens.	

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Polivy is not similar to Imnovid, Farydak, Ninlaro, Darzalex, Kyprolis, Blenrep, Abecma and CARVYKTI within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

5. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Nexpovio-H-C-5127-II-0001/G'