28 January 2021
EMA/CHMP/95252/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nexpovio

International non-proprietary name: selinexor

Procedure No. EMEA/H/C/005127/0000

Note

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
ACN	acetonitrile
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
BCLPD	bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab
BCPD	bortezomib, carfilzomib, pomalidomide, and daratumumab
C1D1	Cycle 1 Day 1
CAR-T	chimeric antigen receptor-T cell therapy
CBR	clinical benefit rate
CHMP	Committee for Medicinal Products for Human use
CI	confidence interval
CLPD	carfilzomib, lenalidomide, pomalidomide, and daratumumab
CPD	carfilzomib, pomalidomide, and daratumumab
CQA	Critical Quality Attribute
CR	complete response
CSR	clinical study report
CT	computed tomography
DCB	duration of clinical benefit
DCR	disease control rate
DIPEA	N,N-Diisopropylethylamine
DoE	Design of experiments
DOR	duration of response
Double-class refractory	refractory to at least 1 proteasome inhibitor and at least 1 immunomodulatory drug (including glucocorticoids)
DSC	Differential Scanning Calorimetry
DVS	Dynamic Vapor Sorption
ECOG	Eastern Cooperative Oncology Group
EU	European Union
FACT-MM	Functional Assessment of Cancer Therapy–Multiple Myeloma
FDA	Food and Drug Administration;
FHAD	Flatiron Health Analytic Database
FLC	free light chain
FMEA	Failure mode effects analysis

Abbreviation	Definition
FT-IR	Fourier transform infrared spectroscopy
GC	glucocorticoid
GC	gas chromatography
GR	glucocorticoid receptor
GTI	Genotoxic Impurities
HDPE	High density polyethylene
HPLC	High performance liquid chromatography
HR	hazard ratio
HRMS	High resolution mass spectrometry
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
Ig	immunoglobulin
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IRC	Independent Review Committee
IR	infrared
Karyopharm	Karyopharm Therapeutics Inc.
KF	Karl Fischer titration
K-M	Kaplan-Meier
LC-MS	Liquid chromatography mass spectrometry
LLDPE	linear low-density polyethylene
MAA	Marketing Authorisation Application
mAb	monoclonal antibody
max	maximum
min	minimum
mITT	Modified Intent-to-Treat [Population]
MM	multiple myeloma
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging
NA	not available; not applicable
NC	not calculable
NE	not evaluable / not estimable
NMR	Nuclear Magnetic Resonance
NR	not reached
ORR	overall response rate
OS	overall survival

Abbreviation	Definition
PCTFE	Polychlorotrifluoroethylene
PD	progressive disease
Ph. Eur.	European Pharmacopoeia
Penta-exposed	prior treatment with bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab
Penta-refractory	prior treatment with bortezomib, carfilzomib, lenalidomide, pomalidomide, and an anti-CD38 monoclonal antibody (either daratumumab or isatuximab) and refractory to at least 1 proteasome inhibitor, at least 1 immunomodulatory drug, an anti-CD38 monoclonal antibody
PET	positron emission tomography
PFS	progression-free survival
PGI	Potential Genotoxic Impurities
PI	proteasome inhibitor
PK	pharmacokinetics
PO	oral
PP	Per-Protocol [Population]
PR	partial response
PS	[ECOG] Performance Status
PVC	Polyvinyl chloride
QoL	quality of life
QTTP	Quality target product profile
Quad-exposed	prior treatment with bortezomib, carfilzomib, lenalidomide, and pomalidomide
Quad-refractory	prior treatment with bortezomib, carfilzomib, lenalidomide, and pomalidomide and refractory to at least 1 proteasome inhibitor and at least 1 immunomodulatory drug
QSAR	Quantitative Structure Activity Relationship
R-ISS	Revised International Staging System
RH	Relative Humidity
RP2D	recommended Phase 2 dose
Rpm	revolutions per minute
RR	relapsed/refractory
RRMM	relapsed/refractory multiple myeloma
SA	single agent
SAP	statistical analysis plan
sCR	stringent complete response
SCXRD	Single crystal X-ray diffraction
Sd	selinexor in combination with low-dose dexamethasone
SD	stable disease
SEM	Scanning electron microscopy

Abbreviation	Definition
SFLC	serum free light chain
SINE	selective inhibitor of nuclear export
SmPC	Summary of Product Characteristics
SPEP	serum protein electrophoresis
STORM	Study KCP-330-012
Triple-class refractory	refractory to at least 1 proteasome inhibitor, at least 1 immunomodulatory drug, and an anti-CD38 monoclonal antibody
Std Dev	standard deviation
TGA	Thermo-Gravimetric Analysis
TOI	trial outcomes index
TSP	tumour suppressor proteins
TTNT	time to next treatment
TTP	time to progression
TTR	time to response
UHPLC	Ultra-high performance liquid chromatography
ULN	upper limit of normal
US	United States
UV/Vis	Ultraviolet/Visible
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Karyopharm Europe GmbH submitted on 9 January 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Nexpovio, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 July 2018.

Nexpovio, was designated as an orphan medicinal product EU/3/14/1355 on 19 November 2014 in the following condition: treatment of plasma cell myeloma.

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 25 February 2021 at the request of the sponsor. The relevant orphan designation withdrawal assessment report can be found under the 'Assessment history' tab on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/nexpovio

The applicant applied for the following indication:

NEXPOVIO, an oral XPO1 inhibitor is indicated in combination with dexamethasone for the treatment of patients with relapsed refractory multiple myeloma (RRMM) who have received at least three prior therapies and whose disease is refractory to at least one proteasome inhibitor (PI), at least one immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody (mAb).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0384/2018 on the granting of a (product-specific) waiver.

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 applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's requests for consideration

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above -mentioned Regulation.

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance selinexor contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
10 November 2016	EMEA/H/SA/2845/3/2016/PA/II	Dr Odoardo Olimpieri Dr Kirstine Moll Harboe
20 September 2018	EMEA/H/SA/2845/4/2018/PA/SME/II	Ms Blanca García-Ochoa Martín Ms Anja Schiel

The Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

The strategy for the selection and control of the starting material; the proposed dissolution method; the design of the registration stability program and stability protocols; the control strategy for potentially genotoxic impurities;

Study design of the Phase 3 confirmatory (KCP-330-023, "BOSTON") trial, including the proposed patient population, the doses and treatment schedule, the choice of primary and secondary endpoints, the choice of instruments to measure patient-reported outcomes, the clinical and statistical rationale for the sample size calculation, and other methodological consideration such as the inclusion of an interim analysis; the adequacy of the safety database for marketing authorisation;

- Whether the single pivotal Phase 3 KCP-330-023 study could support a conditional marketing authorisation based on ORR as primary endpoint, with confirmation of a benefit based on PFS data in the final analysis.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jorge Camarero Co-Rapporteur: Sinan B. Sarac

In June 2020, the Rapporteurship was transferred to Blanca Garcia-Ochoa.

In May 2020, Blanca Garcia-Ochoa was appointed Rapporteur to the application at a late stage replacing the previous Rapporteur from the same national competent authority. For the appointed rapporteur it was considered exceptionally justified that the individual had previously been acting as coordinator for Protocol assistance on the quality and pre-clinical development of the product subject to the present application.

The initially appointed rapporteur and the appointed co-rapporteur had no such prominent role in protocol assistance relevant for the indication subject to the present application.

The application was received by the EMA on	9 January 2019
Accelerated Assessment procedure was agreed-upon by CHMP on	13 December 2018
The procedure started on	25 January 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	2 April 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	22 March 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	02 April 2019
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting o	11 April 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 April 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	05 August 2019
The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Safety/Efficacy assessment of the product:	
– A GCP inspection at 2 investigator sites in Greece and USA and the sponsor site in USA in March 2019. The outcome of the inspection carried out was issued on	24 June 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	04 September 2019

The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	05 September 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	19 September 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	30 December 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	17 January 2020
The CHMP agreed on a 2nd list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	30 January 2020
The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on	15 September 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	06 October 2020
The CHMP agreed on a 3rd list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	15 October 2020
The applicant submitted the responses to the CHMP 3rd List of Outstanding Issues on	11 November 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	26 November 2020
SAG Oncology was convened to address questions raised by the CHMP on The CHMP considered the views of the SAG Oncology as presented in the minutes of this meeting.	30 November 2020
The CHMP agreed on a 4th list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	10 December 2020
The applicant submitted the responses to the CHMP 4th List of Outstanding Issues on	04 January 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	18 January 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Nexpovio on	28 January 2021
The CHMP adopted a report on similarity of Nexpovio with Imnovid, Farydak, Ninlaro, Darzalex, Kyprolis and Blenrep on	28 January 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Nexpovio was proposed to be indicated in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received three prior lines of therapy including an anti-CD38 antibody, a proteasome inhibitor, and an immunomodulatory agent (IMiD).

2.1.2. Epidemiology

Multiple myeloma (MM) is a rare and incurable disease of the plasma cells which typically affects adults who are more than 60 years of age (median age is at diagnosis is ~ 70 years). It is the second most common haematological malignancy (after non-Hodgkin's lymphoma [NHL]), representing 1% of all cancers and 2% of all cancer deaths. In 2018, the estimated annual, age-standardised, MM incidence rate worldwide was 1.7 per 100,000 (Ferlay, 2019). Progress has been made over the last 15 years in the treatment of multiple myeloma, such 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).

2.1.3. Biologic features

Multiple myeloma is characterised by marrow plasmacytomas (plasma cell tumours) and overproduction of monoclonal immunoglobulins (IgG, IgA, IgD or IgE) or Bence-Jones protein (monoclonal K or h light chains), while the production of normal immunoglobulin is impaired.

Based on karyotype, MM is classified as nonhyperdiploid and hyperdiploid, with the latter accounting for 50% to 60% of cases and characterised by trisomies in odd chromosomes. MM has a heterogeneous progression pathway, whereby several MM cell subclones coexist at baseline and compete for dominance over time, leading to the evolution of drug-resistance clones [Laubach, 2014]. Thus, 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). Therapies with a multi-modal mechanism of action (MoA), that both target MM cells and elicit an immunogenic response are expected to minimise development of drug resistance in MM.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The clinical features of MM are varied and can arise from the effects of the tumour itself, or the toxicity of the tumour products, or the host's own immune response.

The most common symptoms include persistent skeletal pain (especially pain in the back or thorax), 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 greater than 10% of BM cells or presence of a plasmacytoma; paraprotein (M-protein)

in the serum and/or urine; and evidence of related organ or tissue impairment due to plasma cell disorder.

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 hybridisation (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 typically categorised 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).

2.1.5. Management

Current treatment of MM includes glucocorticoids (dexamethasone, prednisolone, methylprednisolone), chemotherapy, primarily alkylating agents, including high dose chemotherapy followed by autologous stem cell rescue (ASCT), proteasome inhibitors (PIs) (such as bortezomib, carfilzomib and ixazomib), immunomodulatory agents (IMiDs) (such as thalidomide, lenalidomide and pomalidomide) and the anti-CD38 mAB daratumumab. Other approved anti-MM agents are only approved in combinations, all of which have shown activity only when used in combination with a PI or IMiD.

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.

In very advanced-stage disease, two other drugs are approved in EU for the treatment of relapsed MM:

- Pomalidomide, the third-in-class IMiD, 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.

- Daratumumab, a monoclonal antibody targeting CD38, was also approved for the treatment of adults with relapsed/refractory MM whose previous treatment included a proteasome inhibitor and an immunomodulatory agent and whose disease worsened after treatment.

With the approval of daratumumab and its wide use in combinations in earlier lines of MM treatment, a new population of patients is created who have become refractory to all available agents (including daratumumab). This population can be referred to as triple-class refractory MM and it encompasses those patients with disease refractory to at least 1 PI, 1 IMiD, and an anti-CD38 mAb (such as daratumumab). These patients have generally been exposed to all 5 drugs that have demonstrated single-agent effect (with or without glucocorticoids), including bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab. Most of these patients have already received alkylating agent therapy, other anti-MM drugs, as well as multiple courses of glucocorticoids, they also have numerous comorbidities and receive multiple concomitant medications.

Considering that there are no available agents of proven clinical benefit for the treatment of patients with triple-class refractory (PIs, IMiDs, and anti-CD38 mAbs) MM, thus there is a clear unmet medical need in this setting.

About the product

Selinexor is an oral, first-in-class, slowly reversible covalent, potent selective inhibition of nuclear export (SINE) compound that specifically blocks exportin 1 (XPO1). Exportin 1 mediates the export of many proteins from the nucleus to the cytoplasm, including major tumour suppressor proteins, and cell cycle and regulators leading to cell cycle arrest and apoptosis in cancer cells (sparing normal cells). Exportin 1 is elevated (2- to 4-fold) in all tumour types tested, including MM, and higher XPO1 levels have been demonstrated to be correlated with poor prognosis and/or resistance to chemotherapies.

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the clinical studies submitted for selinexor. Selinexor in combination with dexamethasone has shown a promising antitumour activity in patients considered refractory to PI, IMiD and daratumumab. Taking into account the current armamentarium of MM and the very few options available in those patients considered penta-exposed, triple-class refractory, as well as the clinical activity of the oral XPO1 inhibitor in this population, selinexor is deemed to have the potential to address the unmet medical and to be of major interest from the point of view of public health.

However, during assessment the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as the applicant requested an extended clock-stop to respond to the List of outstanding Issues.

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data. The applicant states that the results from the global phase 3 randomised, active comparator-controlled clinical trial will be available in a timely manner. The phase 3 (BOSTON) study compare the efficacy and assess the safety of selinexor plus bortezomib plus low-dose dexamethasone (SVd) versus bortezomib plus low dose dexamethasone (Vd) in 402 adult patients with RRMM who have received 1 to 3 prior anti-MM regimens. After PD is confirmed by an Independent Review Committee (IRC), patients in the Vd arm may cross over to SVd or Sd treatment. Progression-free survival is the primary endpoint. Patients will be followed for survival until the end of the study. This study will be completed as a confirmatory study and will mainly provide comparative safety data. It will provide less support from an efficacy perspective considering that Sd is given in combination with bortezomib in a prior line of treatment but overall results from the BOSTON study could suffice to address remaining uncertainties and to allow the switch from CMA to full approval for Sd in the applied indication.
- Unmet medical needs will be addressed, as during clinical studies the ORR was 25.3% in patients with penta-refractory multiple myeloma. This is selinexor target patient population for which no other approved therapies exists. Despite the increased number of effective treatment options in the last 20 years, multiple myeloma remains incurable, and nearly all patients will eventually relapse and develop disease that is refractory to all approved anti-MM therapies that have demonstrated clinical benefit in randomised trials. In addition, with each subsequent line of therapy, the duration of response becomes increasingly shorter. As no therapy, including the recently approved belantamab mafodotin, is curative or even effective for the entire population, essentially all patients with MM will eventually need further therapies. Without new therapies

targeting novel mechanisms, these patients quickly succumb to the disease. Therefore, there continues to be a high unmet medical need for new therapies, particularly those with novel mechanisms that can induce rapid disease control and responses in patients with MM whose disease is refractory to the available classes of drugs.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 20 mg of selinexor as active substance.

Other ingredients of the tablet core are: microcrystalline cellulose (pH-101) (E460i), croscarmellose sodium (E468), povidone K30 (E1201), colloidal silicon dioxide (E551), magnesium stearate (E470b), microcrystalline cellulose (pH-102) (E460i) and sodium lauryl sulfate (E514i).

Other ingredients of the tablet coating are: talc (E553b), poly(vinyl alcohol) partially hydrolysed (E1203), glyceryl monostearate (E471), polysorbate 80 (E433), titanium dioxide (E171), macrogol (E1521), indigo carmine aluminium lake (E132) and brilliant blue FCF aluminium lake (E133).

The product is available in PVC/PCTFE/PVC-aluminium blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of selinexor is (2Z)-3-{3-[3,5-bis(trifluoromethyl)phenyl]-1H-1,2,4-triazol-1-yl}-N'-(pyrazin-2-yl)prop-2-enehydrazide corresponding to the molecular formula C17H11F6N7O. It has a molecular mass of 443.31 g/mol and the following structure:

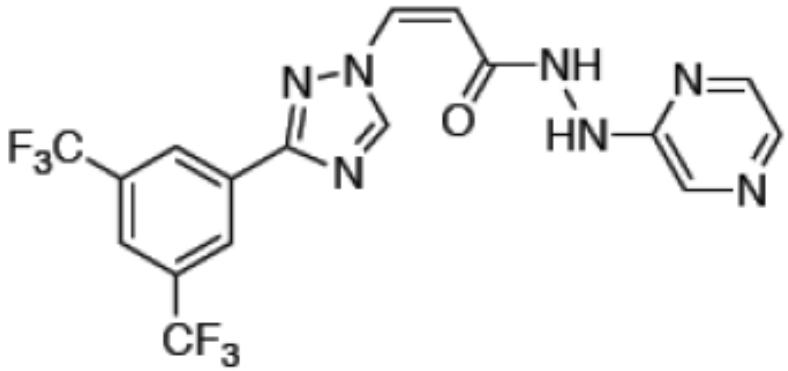


Figure 1: active substance structure

Full information on the active substance has been provided in the dossier. The chemical structure of selinexor was inferred from the route of synthesis and elucidated by a combination of Fourier-transform infrared (FT-IR) spectroscopy, nuclear magnetic resonance spectroscopy (NMR), elemental analysis, high resolution mass spectrometry (HRMS) and ultraviolet/visible (UV/Vis) absorption spectroscopy.

The solid-state properties of the active substance were measured by x-ray powder diffraction (XRPD) analysis, single crystal x-ray diffraction (SCXRD), thermogravimetric analysis (TGA), analysis by scanning electron microscopy (SEM), dynamic vapor sorption (DVS) and differential scanning calorimetry (DSC).

The active substance is a white to off-white powder. It is non-hygroscopic, and is hydrophobic. Hygroscopicity is not considered a critical quality attribute. Selinexor has minor light sensitivity and it has a non-chiral molecular structure.

Selinexor is the *cis* (*Z)* olefin isomer (2*Z*)-3-{3-[3,5-bis(trifluoromethyl)phenyl]-1*H*-1,2,4-triazol-1-yl}-*N*'-(pyrazin-2-yl)prop-2-enehydrazide. The amount of *trans* isomer in the active substance is also monitored in the release specifications via the ultra-high performance liquid chromatography (UHPLC) related substances/total purity method.

Selinexor exhibits pH dependent solubility in aqueous media. At the highest therapeutic dose strength (100 mg), selinexor is not soluble in 250 mL or less in HCl solutions and aqueous media (pH 1.0, 3.0, 5.0, and 7.4) at 37 °C. Solubility values ranged from a low of ~9 µg/mL at pH 7.4 to a high of ~144 µg/mL at pH 1.0. The minimum amount of aqueous media at 37 °C to solubilise 100 mg of selinexor is >690 mL (at pH 1.0).

A permeation assay study was performed on selinexor using metoprolol and atenolol as high and low permeability control compounds in Caco-2 cells. Results indicated that, once in solution, selinexor bioavailability was not limited by its permeability. Selinexor is determined to be a low solubility, high permeability drug (BCS class 2).

Polymorphism has been observed for selinexor. All selinexor active substance used throughout the development and manufactured for human use has been in the most stable polymorph, form A. This form has suitable flow properties for a dry granulation tablet formulation, and it is controlled in the active substance specifications.

Form A is the most thermodynamically stable and the dominant form arising from aqueous and non-aqueous solvent mixtures except acetonitrile (ACN) and nitromethane which form solvates (Forms D and E respectively). Form D is a weakly bound ACN solvate. Drying and thermal experiments were found to convert Form D to metastable partially crystalline Forms B (MP ~91 ºC) and C (MP~155 ºC). Forms B and C thermally convert to Form A in the solid state with heating and in all cross-slurry experiments. Aqueous solubility data on Forms B, C, and D, are not available due in part to their rapid conversion to Form A under aqueous solvent conditions. Form D is isolated as an intermediate in the manufacture of selinexor because it can be isolated from acetonitrile in which relevant impurities are sufficiently soluble to be purged.

After ACN crystallisation of the active substance, Form D is isolated and dried, and is readily converted to Form A in an isopropyl alcohol/water solvent mixture. The properties of crystalline Form A are such that the finished product manufacturing conditions are not expected to impact the polymorphic form. The finished product is manufactured using a dry granulation process without solvents.

Polymorph is a critical quality attribute and is controlled at the active substance specification and has been monitored during finished product stability studies.

Manufacture, characterisation and process controls

The active substance is obtained from a single manufacturer.

The manufacturing process for selinexor consists of four stages using well defined starting materials with acceptable specifications: stage E2 (triazole annulation), stage A1/A2 (conjugate addition and saponification), stage A3 (amide coupling) and stage A4 (polymorph conversion).

Numerous structural alerts exist for potential impurities of the active substance, including those impurities found (actual or potential) in KPT-459, the starting material introduced in the last synthetic step. A major objection was raised during the procedure regarding designation of this starting material. The applicant has provided sufficient data to demonstrate that the overall control strategy is adequate and capable to producing an active substance of high quality, fully in line with ICH Q3A and ICH M7 guidelines, without re-defining this starting material as an intermediate.

The critical part of the acceptance is related to use of KPT-459 in the non-pharmaceutical market. There are numerous suppliers that provide KPT-459 in kilogram quantities for use in non-pharmaceutical markets.

In addition, the synthesis of KPT-459 and the manufacturing process of the active substance are sufficiently understood, and all the controls needed have been implemented in order to obtain a selinexor active substance of sufficient quality from the starting KPT-459 material. The proposed starting material KPT-459 is therefore acceptable. Starting materials KPT-482 and KPT-472 are introduced early in the synthesis with sufficient number of steps post-introduction and are also in line with ICH Q11. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Regarding genotoxic impurities, initial assessments were performed using a QSAR software (LeadScope) and positive findings were assessed by Ames testing. Several impurities were assessed as LeadScope positive but classified as non-mutagenic based upon their structural relationship to a compound which had been determined to be non-mutagenic through Ames testing. An additional assessment using theoretical purge factors was completed allowing no additional controls for these impurities which are controlled according to ICH M7 option 4.

The proposed specification limits for individual potentially mutagenic impurities are below the acceptable intake calculated according to ICH M7 methodology. Suitably sensitive analytical methods have been developed and validated for these impurities, with acceptable LOD and LOQ. Testing results for registration and validation batches are satisfactory.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified.

A risk-based approach is used for the development of the selinexor manufacturing process. The manufacturing process does not include any design spaces; however, aspects of an enhanced approach including the definition of critical quality attributes (CQAs), risk assessment, design of experiments (DoE) and determination of proven acceptable ranges (PARs) are employed. Finally, a control strategy is defined to ensure process performance and active substance quality. The Applicant ensures that "the manufacturing process will be conducted within the normal operating ranges (NORs) for all process parameters, with excursions into the PAR for only a single parameter at a time".

The active substance is packaged in double linear low-density polyethylene (LLDPE) bags placed into a heat-sealed foil pouch and then into a high-density polyethylene (HDPE) drum closed with a gasket-lined, HDPE screw cap. Primary packaging material complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: appearance (visual), identification (IR, UHPLC, XRPD), assay (UHPLC), related substances (UHPLC), residual reagents (GC) residual solvents (GC), residual hydrazine content (HPLC), residual KPT-459, KPT-534, and KPT-548 (LC-MS), residual KPT 460, and KPT-550 (LC-MS), total GTI/PGI residuals (LC-MS), water content (KF), elemental impurities (ICP-MS), residue on ignition (Ph. Eur.), particle size distribution (light diffraction) and microbial quality (Ph. Eur.).

The active substance specifications are based on the active substance CQAs. The CQAs identified are: identification, assay, related substances, specified and unspecified impurities, residual reagent N,N-diisopropylethylamine (DIPEA), residual solvents, residual hydrazine, residual product-related impurities and total GTI/PGI residuals, elemental impurities, crystalline form, and container closure.

All possible process impurities in the synthesis of selinexor which were found to be Ames positive and are categorised by ICH M7(R1) consensus as mutagenic class 2. In addition, the known class 1 carcinogen, hydrazine, is a reagent in the manufacturing process.

Liquid chromatography – mass spectroscopy/mass spectroscopy (LC-MS/MS) methods have been developed and validated to monitor the limits of the five 5 Ames positive impurities of selinexor. Specifications have been set and are monitored in the registration stability testing.

The current limits for individual genotoxic impurities in selinexor were calculated according to a chemical-specific risk assessment. The limits are based on an excess cancer risk of 10^{-5}, taking into consideration the potential benefit of the drug and the nature of the patient population (i.e., patients with advanced haematological malignancies). While the ICH M7 guidance, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, specifically excludes agents intended for the treatment of advanced cancer as part of its scope, the principles contained in this guidance were considered in the current assessment of selinexor.

The total genotoxic/potential genotoxic impurities limit for the six (6) priority impurities has been set. Based on ICH M7(R1) guidance, the proposed calculation and limit is well justified and represents a tighter specification than the ICH M7 allowable total. It ensures tighter control than the sum of the allowable individual limits, and that no combination of impurities within specification or below the LOQ can result in a sum greater than the guidance limit.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on three consecutive commercial scale batches of the active substance are provided. In addition, results for batches manufactured by the previous manufacturer used for clinical and development studies have also been provided. Batch results indicate a consistent production process. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 4 pilot and 3 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* appearance, identification and polymorphic identity, assay, individual impurities, total impurities, water content, product-related impurities, microbial limit test and

specified microorganism. The analytical methods used were the same as for release and are stability indicating.

All tested parameters were within the specifications. No significant changes or trends were observed.

Samples were also stored under stressed conditions (100 °C / ambient (RH) for 24 hours, high heat/humidity at 50 °C / 75% RH, high heat at 60 °C. KPT-375 was the only potential degradation product that was produced in the forced degradation studies. It was also observed in very small amounts (0.05-0.09% w/w) under long-term storage conditions up to 48 months and under accelerated storage conditions up to 6 months for both registration and stability batches.

Photostability testing following the ICH guideline Q1B was performed on a single batch. The results from the photostability studies indicate that selinexor is slightly susceptible to light and that protective packaging should be used for storage.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period and storage conditions "do not store above 25 ºC" in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is formulated as immediate release tablets for oral administration. Nexpovio tablets are blue, bi-convex, round, film coated tablets with "K20" debossed on one side and nothing on the other. Tablets are 4 mm thick and 7 mm in diameter.

Pharmaceutical development of the finished product contains QbD elements.

The CQAs identified were crystalline/polymorph form of selinexor in the tablet, identification, assay, impurities and degradants, content uniformity, dissolution, and microbial burden.

The physicochemical properties of the active substance that could influence the performance of the finished product and its manufacturability were identified and discussed.

Selinexor exhibits poor aqueous solubility and rapid transport across membranes. Research and development tablets were manufactured with active substance of various particle size distribution profiles in order to obtain different dissolution or drug release profiles.

In general, active substance particle size and particle size distribution can lead to content uniformity and flow-related processing issues. Although selinexor is not milled, it represents 12.5% of the tablet formulation, and the tablets are manufactured using a dry granulation process that can minimise the impact of selinexor particle size and particle size distribution on downstream processing. Particle size and particle size distribution within the proposed limit was not identified as a CQA for selinexor tablets.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards with the exception of Opadry 200 Clear and Opadry II Blue. However, these two non-compendial film coating materials are well-known and composed of only compendial components. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The compatibility of selinexor with the excipients has been demonstrated. Multiple binary mixture studies between selinexor and excipients of the tablet formulation were performed under accelerated

conditions to evaluate the compatibility of the excipients with the active substance. Results indicated minimal or no impurity formation of selinexor with the tablet excipients.

The formulation and manufacturing development have been evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical process parameters. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. The critical process parameters have been adequately identified. Design of experiments (DoE) studies were conducted on the dry granulation formulation to evaluate the effects of the selected excipients on the manufacturability and CQAs of selinexor tablets.

During development, two different finished product manufacturers were involved. Selinexor formulations developed for clinical studies through commercial scale included capsules, wet granulated tablets (Tablet Formulation 1 or TF1) and dry granulated tablets (Tablet Formulation 2 or TF2). All three formulations met with acceptance criteria for release and stability and demonstrated equivalent pharmacokinetic parameters in humans (comparative Phase I bioavailability clinical study in patients). The Opadry II Blue 85F90982 film coat used in the TF2 formulation (designated TF2.2) contains FD&C Yellow #5 (tartrazine aluminium lake), an ingredient that may cause allergic reactions. Therefore, a tartrazine-free Opadry II Blue (85F90892) film coat was selected for the commercial finished product formulation, designated TF2.3. The presence or absence of tartrazine aluminium lake does not affect the dissolution of selinexor tablet, or the stability of the product. The two formulation variants are considered equivalent.

During product development, high speed homogenised/freeze-dried selinexor capsules, low-shear wet granulation tablets (TF1), high-shear wet granulation tablets, and dry granulation tablets (TF2) were evaluated. The high speed homogenised/freeze-dried selinexor capsules and low-shear wet granulation tablets (TF1) were manufactured to support the early phase clinical studies. Ultimately, the dry granulation tablets (TF2) final formulation was developed and manufactured at clinical, pilot and commercial scales to support expanded clinical studies, registration stability studies, and product commercialisation.

For an active substance of low solubility and high permeability, the disintegration and dissolution rate of the tablet may impact the rate the absorption and bioavailability. Therefore, Nexpovio 20 mg film-coated tablets were designed to disintegrate rapidly in the stomach and upper gastrointestinal tract to ensure absorption. The dissolution method uses a Ph. Eur. paddle apparatus. At the request of CHMP, the dissolution limit was tightened to Q=80% in 30 minutes during the procedure, in order to ensure that the method is sufficiently discriminatory and appropriate for control of the finished product.

Although a predictive relationship between *in vitro* dissolution of selinexor tablet and *in vivo* response has not be established, a highly discriminating dissolution method has been developed which is sufficiently able to discriminate between physical changes in the finished product (e.g. varying active substance particle sizes, exclusion of disintegrant excipient, varying lubricant level and lubrication blend time).

The primary packaging is PVC/PCTFE/PVC-aluminium blisters. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

Nexpovio is formulated as an immediate release film-coated tablet and manufactured using a typical dry granulation process. The manufacturing process consists of six main steps: pre-compaction de-lumping / blending, dry granulation, final blending, tablet compression, tablet coating and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies on three commercial scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), package appearance (visual), identification (HPLC-UV, HPLC), assay (HPLC), impurities (HPLC), content uniformity (HPLC), dissolution (HPLC), water content (KF), microbial enumeration test (Ph. Eur.) and tests for specified microorganisms (Ph. Eur.).

A test for hardness is not included in the finished product specifications as hardness is not considered a CQA for Nexpovio film-coated tablets. This test is conducted as an in-process control on the tablet cores during tablet compression. Throughout development, the variation of tablet hardness did not show an effect on dissolution parameters.

With the use of the thermodynamically favoured Form A and no observed change in polymorphic form during the finished product stability studies, it was not necessary to set testing and acceptance criteria for the polymorph identity in the release specifications.

Based on risk assessment, the testing of residual solvents content in the finished product does not add to the control of quality for Nexpovio 20 mg tablets and, in accordance with ICH Q3C, testing for residual solvents is not proposed as part of the finished product batch release specification.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed as requested considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results were provided for two commercial scale batches of the intended commercial formulation. Supportive data from 28 development batches was also provided and the results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from three pilot scale batches of finished product stored for up to 36 months under long term conditions (5ºC / 60% RH, 25ºC / 60% RH and 30ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

Additional supportive data was presented from three commercial scale batches stored for up to 6 months under long term conditions (5ºC / 60% RH, 25ºC / 60% RH and 30ºC / 60% RH) and accelerated conditions (40ºC / 75% RH).

Further supportive data was presented on 2 pilot scale batches and 2 commercial scale batches stored for up to 48 months under long term conditions (5ºC / 60% RH, 25ºC / 60% RH) and intermediate conditions (30ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH).

All of the above-mentioned batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging representative to the one proposed for marketing.

Samples were tested for the same parameters as for release, except for content uniformity. The analytical procedures used are stability indicating.

All stability study results demonstrate the chemical and physical stability of selinexor tablets under all storage conditions. The results of long-term and accelerated stability studies demonstrate the chemical and physical stability of selinexor tablets when stored for up to 44 months under long-term and intermediate conditions and for up to 6 months under accelerated storage conditions. There were no significant changes or trends observed in the physical appearance, assay, polymorphic identity, drug-related impurities, hardness, dissolution or water content in the long-term studies and all results were within specifications.

Nexpovio tablets in bulk configuration demonstrated stability for up to 36 months for registration batches at controlled room temperature and up to 3 months at 40°C / 75% RH. There were no significant changes or trends observed in the physical appearance, assay, polymorphic identity, drug-related impurities, hardness, dissolution or water content in the long-term studies and all results were within specifications.

In addition to the long-term studies, data were presented following short-term storage of the finished product under a range of stressed conditions. Samples were exposed to a range of conditions including thermal stress (60°C/Ambient RH), acid/base hydrolysis, H_2O_2 oxidation, intense light to determine photostability, freeze-thaw temperature cycling, high heat/humidity and in open bottles. There were no significant differences between the peak purity results from the control and stressed samples, indicating that there were no degradation products generated under these stress conditions, the finished product is considered stable under each of these conditions. Forced degradation studies on selinexor tablets were performed both in the solid and solution phase.

The results of studies with finished product packaged in blisters and exposed to stressed conditions including high heat/humidity and high heat were consistent and met specifications. The results from the freeze-thaw temperature cycling stability study indicate that the finished product remains of high quality when exposed to environments that include temperature cycles of extreme cold (-20°C) and high heat and humidity (40°C / 75% RH) when packaged in either blister or bulk packaging. These data support the choice of the bulk and blister packaging as a robust proposed commercial packaging system.

A photostability study was performed on selinexor stored in blister packages with dark control samples overwrapped with aluminum foil. At the end of the 8-day photostability study under ICH Q1B Option 2 conditions (LUX/UV light conditions (fluorescent light (NLT 1.2 million lux-hours) and UV light (NLT 200 watt hours/m^2) there was very little difference between the results of the dark control and exposed test materials. All results were found to be well within specifications. The results from the photostability study indicate that the finished product is not sensitive to light exposure and does not require special packaging to protect it from light.

Based on available stability data, the proposed shelf-life of 36 months as stated in the SmPC (section 6.3) is acceptable. This medicinal product does not require any special storage conditions.

Adventitious agents

No excipients derived from animal or human origin have been used. Magnesium stearate is of herbal origin.

Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Sufficient data has been presented on control of nitrosamine impurities.

Following a major objection raised on designation of one of the starting materials, sufficient data was provided in order to justify the designation and the major objection was resolved.

A second major objection was raised during the procedure on the specification limits for dissolution of the finished product. In order to assure the discriminatory power, dissolution limits were tightened and the major objection was resolved.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Sufficient data has been presented on control of nitrosamine impurities.

Following a major objection raised on designation of one of the starting materials, sufficient data was provided in order to justify the designation and the major objection was resolved.

A second major objection was raised during the procedure on the specification limits for dissolution of the finished product. In order to assure the discriminatory power, dissolution limits were tightened and the major objection was resolved.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions

defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Primary and secondary pharmacology studies described in this section were conducted in accordance with accepted practice for these study types and in general agreement with the principles of Good Laboratory Practice (GLP).

The effect of selinexor was shown both *in vitro* and *in vivo* studies in different experimental models of cancer.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The pharmacodynamic studies were conducted to show the potential pharmacological actions of selinexor via binding to XPO1, inhibition of XPO1-mediated nuclear transport of tumour suppressor proteins and growth regulatory proteins; and cycle arrest and killing of tumour cells. The pharmacological characterisation was based on both *in vitro* and *in vivo* experimental models.

- *In vitro* studies

Selinexor (KPT-330) has been developed as an oral specific inhibitor of exportin-1 (XPO-1), a protein that mediates the nuclear export of proteins and RNA. XPO-1 binds cooperatively to proteins containing a nuclear export sequence (NES), including a variety of transcription factors and tumour suppressor proteins (TSPs). Overexpression of XPO1 has been suggested to occur in a variety of malignancies including multiple myeloma where it has been linked to resistance to therapy and poor survival. It is hypothesised that inhibition of XPO-1 by selinexor will lead to the nuclear accumulation of TSPs, such as p53, resulting in the growth arrest and cell death of the cancer cells.

XPO1 occupancy by selinexor in in-vitro experimental systems was estimated to be about 50% and 90% of at 20 nM and 480 nM, respectively. These levels of occupancy were obtained in murine PBMC after treatment of animals with 3 mg/Kg and 10 mg/Kg, respectively. As part of the *in vitro* characterisation, selinexor induced the nuclear localisation of TSPs and GRPs (p53, p21, FOXO3a, APC, FOXO1a, IκB, p27, PP2Aα, and Survivin) and the inhibition of proto-oncogenic mRNAs (cyclin D, cyclin E, Pim1, ODC, c-Myc, Bcl-2 and Bcl-6) regulated by eIF4E. An additional action was also proposed by decreasing DNA synthesis and inducing cell cycle arrest. An increase of XPO1 mRNA levels, which was not accompanied by XPO1 protein expression was shown. It is noted that selinexor induced XPO1 protein degradation, reported as proteasome-mediated degradation (Tai et al., 2014).

The Applicant justified the dose level of 60 to 80 mg in humans based on the occupancy level of XPO1 receptor reported in mice. According to the data provided, the dose level of 10 mg/Kg in mice (30 mg/m2) given three times weekly, corresponds to the human dose of 50 mg, which exhibited a 90% of

receptor occupancy of XPO1 for 6 hours post dose. However, most studies presented were conducted in mice at the dose level of 5 mg/Kg showing efficacy, although a significant reduction in body weight was also observed. Moreover, the applicant proposed to use XPO1 mRNA induction as a biomarker of the activity for selinexor, although this effect was not followed by protein expression. Maximum activity was shown at 12 mg/m^2 (study KS-50001). The Applicant reported that the increase in mRNA is a biological feedback loop in response to the inhibition of nuclear export.

The cytotoxic effect of selinexor on cancer cell lines was observed in: multiple myeloma; Non-Hodgkin's lymphoma; and acute myeloid leukaemia and acute lymphoblastic leukaemia cells. The results showed IC_{50} values ranged from 20 to 434 nM; 12 to 441 nM; and from 21 to 203 nM, respectively. In the case of multiple myeloma cells, the applicant proposed two additional actions of selinexor based on publications. One of them was the stabilisation of IκB-α by inhibiting its phosphorylation and degradation, resulting in the inhibition of NF-κB transcription activity. The other one was an increase in GR protein levels, resulting in the inhibition of the mitogenic and inflammatory NF-κB pathway.

- *In vivo studies*

Pharmacodynamic effects of selinexor were shown in in-vivo models of cancer, both as single agent and in combination with other anticancer agents. Selinexor was tested in MM1.S or H929 myeloma cells in NOD-SCID mice. When used as a single agent at doses ≥15 mg/kg twice or three times weekly, selinexor was seen to inhibit the observed growth of the implanted tumours. Selinexor alone dosed at 5 mg/kg (3 times weekly) did not modulate tumour growth, however, when used in addition to dexamethasone the combination effectively prevented growth of both MM1.S or H929 melanoma tumours in NOD-SCID mice. Moreover, effects on tumour growth of selinexor with lenalidomide and with the proteasome inhibitor, bortezomib was seen in the same study of MM1.S tumours in NOD-SCID mice (KS-0070). No survival data or Kaplan Meier curves have been presented. Mouse models of haematological malignancies (Mantle Cell Lymphoblastoid Lymphoma (Z-138), Acute Lymphoblastic Leukaemia (MOLT-4), AML (MV-4-11), or AML (MOLM-16)) were also used to test the effects of selinexor. In all of them, treatment with selinexor induced the reduction of tumour volume, although significant weight loss was also reported as indicative of toxicity.

The other part of the *in vivo* studies was related to the results obtained with other treatments (dexamethasone, lenalidomide, proteasome inhibitors or panobinostat) in combination with selinexor in multiple myeloma mouse models. In all of them, treatment with selinexor in combination resulted in an increased reduction of tumour volume. It should be noted that animals receiving selinexor as monotherapy showed less significant body weight reduction than in the case of the combination with dexamethasone. However, contradictory effects on body weight were observed in animals dosed with selinexor as monotherapy or KPT-330 plus dexamethasone in studies KS-0085 and KS-0070.

Secondary pharmacodynamic studies

Selinexor was tested in other potential pharmacological effects than the primary pharmacodynamics actions described in the previous section. In this regard, its selectivity was profiled in 112 human and rat receptor-binding or enzymatic assays (study KS-0034). The final concentration was 10μM and tested in duplicate. In addition, two functional assays were incorporated to the secondary pharmacodynamic studies (KS-0065 and KS-0066).

Activity of selinexor was detected in the case of: Kinase Protein AurA (Aur2/STK6) (h) 40%; Kinase Protein p70s6k (h) 42%; and Oxidase, MAO-B, Central 50%. According to the screening assays interpretation, compounds showing inhibition of 50% or greater could be qualified. The Applicant conducted a study in which selinexor was tested in a MAO-B recombinant enzyme assay (KS-0066). No

IC_{50} was estimated, as concentration-response curve showed less than 25% effect at the highest validated testing concentration.

Safety pharmacology programme

Safety pharmacology studies were conducted with selinexor, in line with ICH S9 guideline. Additional endpoints were incorporated in the repeated dose toxicity studies.

Cardiovascular system

In vitro: the effect of selinexor on hERG current was evaluated in a GLP-compliant study (KS-0055). hERG current was significantly inhibited by selinexor ($p<0.05$) when compared to control group ([mean ±SEM] 3.9±0.8% at 1 μM (n=3), 10.4±0.8% at 3 μM (n=3), 31.4±1.1% at 10 μM (n=3), and 60.1± 0.5% at 30 μM (n=3) versus 0.8±0.3% (n=5) in control). Under identical conditions, the positive control (60 nM terfenadine) inhibited hERG potassium current by [mean±standard deviation (SD)] 87.8±4.3% (n=2). The IC_{50} for the inhibitory effect of selinexor on hERG potassium current was 20.6 μM (Hill coefficient=1.1). The Applicant estimated >250 times safety margins based on the human free unbound C_{max} following an 80 mg dose (0.033 μg/mL; based on human plasma protein binding of 95.1% and mean C_{max} of 0.68 μg/mL).

In vivo: potential *in vivo* actions of selinexor on cardiovascular system were incorporated in the GLP 4-week (KS-0047) and 13-week (KNC-G-13-002) toxicity studies in monkeys. No effects were observed on cardiovascular function in both studies at the maximum dose level tested, i.e. selinexor at ≤3mg/Kg given 3 times weekly in the 4-week study (combined sex mean AUC_{last} of 5.89 μg.hr/mL and mean C_{max} of 0.83 μg/mL); and selinexor at ≤1mg/Kg/day given 2-3 days per week (combined sex mean AUC_{last} of 1.51 μg.hr/mL and mean C_{max} of 0.24 μg/mL).

Central Nervous system

Selinexor (0, 2, 10, or 50 mg/kg) was orally given (single-dose) to male rats in a GLP study (KS-0051) to evaluate the effects on CNS through the Irwin test. No effect was reported at the lowest dose levels, i.e. 2 and 10 mg/Kg. On the contrary, animals given with 50 mg/Kg exhibited a significant decrease of body temperature (0.9ºC; $p<0.05$) and respiratory difficulty. The Applicant attributed this effect to the reduction in pyrogenic cytokines (IL-1, IL6 or TNF-α). NOEL value was established at 10 mg/Kg.

Respiratory system

Respiratory function (respiratory frequency, tidal volume, and minute volume) was evaluated after administration of a single-dose of selinexor in a non-GLP study (KS-0054). Male rats received selinexor at 0, 2, 10 or 50 mg/Kg. The Applicant considered the NOEL value 2 mg/Kg, given that a dose-dependent significant reduction ($p<0.05$) in minute volume, respiratory frequency, and tidal volume was observed at ≥10mg/Kg.

Pharmacodynamic drug interactions

No pharmacodynamic (PD) drug interaction studies with selinexor have been submitted.

2.3.3. Pharmacokinetics

Absorption, elimination, metabolism and biodistribution properties were studied in *in vitro* and *in vivo* models. Pharmacokinetic profile of selinexor was analysed in mouse, rat, dog and monkey, both in single- and repeated-dose studies. Additional *in vitro* studies were conducted to further characterise

the properties of selinexor. In this regard, permeability was evaluated in Caco-2 cells, plasma protein binding and *in vitro* metabolism were also analysed.

The applicant has presented a summary of the methods used for the analysis of selinexor concentrations in both rat and monkey plasma samples. Validation was undertaken in compliance to GLP standards and is broadly in line with the EMA 'Guideline on bioanalytical method validation' (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2). Analyte concentrations are expressed in terms of ng/ml.

In terms of potential permeability, the applicant reported selinexor as not a substrate for P-gp or BCRP in the pharmacokinetics written summary.

Single dose studies were conducted in mouse, rat, dog and monkey. In the case of monkeys, the potential effect of formulation changes and food on pharmacokinetic parameters were analysed. It was concluded that food could affect C_{max} and T_{max} parameters, by increasing T_{max} and reducing C_{max}, but it did not modify significantly the exposure (AUC) in monkeys. Tablets and gelatine capsules containing selinexor also showed different C_{max} and T_{max}, although overall exposure was not significantly modified. Repeated dose toxicokinetic studies were carried out in satellite groups of animals. A dose dependent increases in systemic exposure were observed in these studies. No or moderate accumulation was observed after repeated dose in monkeys and rats treated for 13 weeks.

PPB studies showed that protein binding of KPT-330 was independent of concentration. The results indicated high bound to proteins in all the species tested (>95%), except in dogs. Given that blood to plasma ratio was less than 1, selinexor is suggested not to be sequestered into red blood cells.

Biodistribution of selinexor after oral administration was assessed in a tissue distribution study (KS-0091). It exhibited the highest levels of radioactivity in small intestine, kidney, stomach, and liver. The lowest level was quantified in skin, uveal tract, spinal cord, testis, bone and eye. Double-peak levels reported in some tissues were attributed to the enterohepatic recirculation by the applicant.

Main metabolites were studied in rats, monkeys and humans. The GSH-related metabolites were majorly detected, with no pharmacological activity, although it is suggested that they contributed to the elimination route. The *in vivo* metabolism was proposed to be cytochrome-P450 mediated and conjugation (phase II) was identified as an important route of clearance.

The applicant reported a possible involvement of CYP3A4 and multiple UGT enzymes in the metabolism of selinexor. As such, it is concluded that selinexor at a dose of 100 mg and Cmax value of 2 µM has the potential to inhibit intestinal CYP3A4.

CYP inhibition studies revealed direct inhibition of CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4/5-mediated testosterone 6β-hydroxylation with IC50 values of 24, ~ 50, 42, 35 and 24 µM, respectively. A biphasic response was seen when CYP3A4/5 was investigated with midazolam as substrate with apparent increases in activity up to 10 µM and then decreased activity at higher concentrations. This effect can be attributed to a possible allosteric interference with the metabolism of midazolam. Based on a Cmax of 2 µM the applicant has argued that selinexor has a low potential for drug interaction due to CYP inhibition.

CYP induction was assessed at levels up to 10 µM owing to cytotoxicity at 30 µM and above. Induction of CYP1A2 was only seen in one of the hepatocyte cultures (HC10-23), however, the response occurred in a dose proportional manner in this culture and similarly in the HC7-12 cultures although at a very marginal level which didn't reach significance. Of note is the very pronounced inhibition of CYP3A4 expression on a mRNA level in 2 of the 3 hepatocyte cultures and to a lesser extent in the third culture. Although there does not appear to be a dose relationship the effects are very pronounced.

However, it is accepted that no accumulation of selinexor was seen following multiple dosing, which would support the conclusion that the decrease in mRNA has no *in vivo* implications.

Studies on *in vitro* transporter inhibition revealed that selinexor was an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, and MATE1 with IC_{50} values of 11.2, 6.20, 35.6, 11.2 and 22.3 μM, respectively. The Applicant calculated the potential for selinexor to inhibit various transporter *in vivo* based on the cut-offs as recommended in the EMA guidance. In this manner, it was concluded that there is no potential for selinexor to inhibit any of the investigated transporters *in vivo*. *In vitro* SLC transporter studies revealed selinexor as a weak substrate of BCRP.

Bile was identified as the major excretory pathway, while urine and faeces were much minor pathways of excretion. It is supposed that excreted content in bile is returned to gastrointestinal tract and then excreted in faeces and urine. Regarding the content of bile, it had the highest levels of selinexor by comparison with urine and faeces, although the concentration of metabolites in bile was greater than selinexor. Additional studies reported that selinexor is minimally excreted in urine.

2.3.4. Toxicology

Single dose toxicity

The applicant determined the MTD value for selinexor at 100 mg/Kg in rat (AUC_{last}= 65.9 μg*h/mL; C_{max}= 15.9 μg/mL) administered by oral gavage (KS-0041, non-GLP). In this study, the dose levels ≥100 mg/Kg produced diarrhoea, recovered on day 2. Microscopic findings (thinness of the GI tract and liquid in the stomach and intestine) were also reported at ≥100 mg/Kg. In the case of animals given at 500mg/Kg, diarrhoea was observed with decreased motor activity and piloerection. Thinness of the GI tract and liquid in the stomach and intestine, and stomach enlargement was also described. Clinical chemistry changes were observed at ≥25 mg/Kg.

A summary of the single dose toxicity studies is included in the table below.

Table 1 Single dose toxicity studies conducted with selinexor

				Test Article: Selinexor			
Species/Strain	**Method of administration (vehicle/ formulation)**	**Doses (mg/kg)**	**Gender and No. per group**	**Observed maximum nonlethal dose (mg/kg)**	**Approximate lethal dose (mg/kg)**	**Noteworthy Findings**	**Study No.**
Rat (Sprague-Dawley)	po, gavage (0.5% Pluronic® F-68; suspension)	0, 25, 100, 500	3M/3F	500	ND	**MTD**: 100 mg/kg **25 mg/kg**: no treatment-related clinical signs or macroscopic findings. **25 and 100 mg/kg**: minimal clinical chemistry changes (↑: LDH and CK (M, F), AST (only F at 100 mg/kg). **100 and 500 mg/kg**: diarrhea [mild (100 mg/kg) to severe (500 mg/kg)], thinness of stomach and intestine wall, stomach and intestine full of liquid contents. **500 mg/kg**: Decreased motor activity (M/F), cold to touch (M only), and piloerection (M/F). Clinical chemistry changes (↑: ALT, AST, LDH, BUN, CREA (M only), CK, and amylase (F only; decreased in M)). Stomach enlargement. **All dose levels:** no mortality, dose dependent decreases in food and water consumption and body weights, and dose dependent changes in clinical chemistry parameters.	KS-0041

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; CREA = creatinine; F = female; LDH = lactate dehydrogenase; M = male; MTD = maximum tolerated dose; ND = not determined; po = oral

Repeat dose toxicity

Pivotal GLP compliant studies of 4 and 13-week duration were performed in both species in line with the requirements set out in ICH S9 for therapies for the treatment of advanced cancers. The applicant established the NOAEL and STD_{10} values for selinexor in rats based on the findings reported in the 13-week repeated dose toxicity study. As such, NOAEL was reported to be 0.25 mg/Kg/day for males and 1 mg/Kg/day for females, which was hardly justified given the severity of the findings reported in the study report. In the case of STD_{10}, it was considered to be between 1 and 4 mg/Kg/day in males and females due to reproductive organ toxicity (males: testes, epididymides, and/or seminal vesicle macroscopic findings, lower organ weights, and microscopic findings; and females: macroscopic findings in the uterus, higher uterus weights, and microscopic findings in the ovaries, vagina, and uterus), which were not reversible.

In the toxicity studies conducted with selinexor in monkeys, gastrointestinal toxicity, decreased body weight and food consumption, uncoordinated movements (day 7) and mortality (day 11) were reported at the dose level of 7.5 mg/Kg. A similar toxicity profile was also reported in another study carried out in monkeys dosed at 6 mg/Kg, in which moribundity and necrosis of granular cells were also observed. The findings reported at this dose could be indicating a central nervous system related toxicity. In another toxicity study (KS-0047), the applicant considered 3 mg/Kg as the MTD for monkeys. However, unscheduled mortality and sacrificed animals for humane reasons were reported at this dose level. Likewise, in this study, the HNSTD was established at 1.5 mg/Kg where severe toxicological findings

were reported with no reversibility (high liver weights, high lipase and amylase values, or body weight loss).

Similarly, the applicant considered the 2.5 mg/Kg dose level as well tolerated in the 2-week study conducted in monkeys (KS-0046). However, significant changes were reported in animals at this dose level, such as alteration of haematology parameters (lower white blood cell, neutrophil, eosinophil, basophil, lymphocyte, monocyte, large unstained cell, red blood cell, and reticulocyte counts, as well as lower haemoglobin and haematocrit values and mean corpuscular volume); lower organ weights (males: epididymides, seminal vesicles, prostate, spleen, testes, and thymus weights; and females: thymus, thyroid/parathyroid, and uterus); or histologic findings (multifocal nephrosis of the kidney, mucosal atrophy of the stomach, lymphoid depletion in peripheral lymph nodes and Peyer's patches of the small intestines, cellular depletion of the spleen, thymus atrophy, glandular atrophy of the salivary gland in females). Not all of them were reversible, and consequently it is difficult to understand how this dose level was considered as tolerated. Last, the applicant considered the NOAEL (and HNSTD) for selinexor as 1 mg/kg from the 13-week toxicity study performed in monkeys. However, lower thymus weights (not recovered) was observed in females at 0.3 mg/Kg and clinical observations at ≥0.1 mg/Kg were reported (inappetence and abnormal excreta (soft faeces and/or diarrhoea) in males and females correlated with thin body condition; and body weight losses and/or lower body weight gains). These animals were fed supplemented to maintain their health status. Whilst no CNS effects were seen in the safety pharmacology studies, necrosis of granular cells was seen in one monkey receiving selinexor at 6 mg/Kg (HED 1.8 mg/Kg) and the study by Chen *et al*., 2018 has suggested that the frequent non-haematological toxicities of fatigue and GI toxicities were most likely centrally mediated. Moreover, additional publications comparing selinexor with other SINE compounds (such as KPT8602), indicates that less anorexia, malaise and weight loss is attributed to a lower penetration across BBB (Etchin et al., 2017; Vercruysse et al., 2017; Wang and Liu 2019).

Another question raised from these studies is the minimal or absence of safety margin for human studies. In this regard, other XPO1 inhibitors (Leptomycin B, KPT-335) have shown an *in vitro* and *in vivo* potency along with a significant toxicity (anorexia, body weight reduction, inappetence…), indicating a potential class toxicity (including hepatotoxicity). The applicant reported nausea and anorexia as class effect for XPO1 inhibitors, including selinexor.

Toxicokinetics measured as part of the repeat dose studies revealed no evidence of differences in exposure between the sexes. The exposure levels at the identified NOAEL in the 13-week study in monkeys is less than the measured exposure at the clinical dose of 80 mg. Indeed, with the exception of the highest dose in the 4-week study in rats of 15 mg/kg and in monkeys of 3 mg/kg there is no margin of exposure from any of the doses in the repeat dose toxicity studies.

Genotoxicity

Potential genotoxicity of selinexor was evaluated in two *in vitro* and one *in vivo* studies.

Bacterial reverse mutation test (KS-0039, GLP)

Genotoxicity of selinexor was evaluated in the bacterial mutation test, by using four S. typhimurium strains (TA1535, TA1537, TA98, TA100) and one E. coli strain WP2 uvrA in the presence or absence of metabolic activation. Selinexor was tested at the concentrations of 1.58, 5.0, 15.8, 50, 158, 500, 1581, and 5000 µg/plate. Cytotoxicity and precipitation were observed in some cases at the highest concentrations, but no increases in revertant colony numbers were reported. The applicant concluded no evidence of genotoxic activity.

Chromosome aberration test (KNC-G-13-005, GLP)

The potential to induce chromosome aberrations in human peripheral blood lymphocytes by selinexor was evaluated in short and long incubations with or without metabolic activation system.

No statistically significant increases in structural aberrations or numerical aberrations (polyploidy or endoreduplication) were observed for selinexor.

Micronucleus test in rat (KNC-G-13-004, GLP)

Micronucleated polychromatic erythrocytes were measured in rat bone marrow after three consecutive days of treatment with selinexor. The initial dosage levels were 2, 15 and 30 mg/Kg/day, but due to the toxicity observed at the highest dose levels (i.e. 15 and 30 mg/Kg/day), a second study with 2, 4, 7, and 10mg/Kg/day was conducted.

No increase of bone marrow micronuclei was reported after treatment with selinexor. However, animals dosed at ≥4mg/Kg/day presented lower food consumption and lower body weight gains and body weight loss.

Carcinogenicity

No carcinogenicity studies with selinexor were submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

No fertility and early embryonic development studies with selinexor were submitted.

In an embryofoetal developmental toxicity study in rats the NOAEL value for maternal toxicity and embryo-foetal development was established at 0.25 mg/Kg/day and the resultant exposures measured represent a margin of exposure of 0.02 from the clinical dose. The Applicant has suggested that based on the findings in rats that studies in a second species are not warranted.

In the definitive GLP study at doses of 0.25, 0.75, or 2 mg/kg/day no effects on mean numbers of corpora lutea and implantation sites, mean litter proportions of pre-implantation loss, or skeletal and visceral foetal morphology. The NOAEL was defined on the basis of lower mean body weight gains and food consumption in the dams and lower foetal weights and skeletal variations in the foetuses.

Local Tolerance

***In vitro* (Bovine corneal opacity and permeability test, GLP)**

Selinexor was evaluated in BCOP test at the concentrations of 10, 100 or 300 μM (studies KS-0098, KS-0099, and KS-0100). No evidence of ocular tissue damage was reported.

***In vivo* (Guinea-Pig sensitisation study, GLP)**

The applicant reported the effect of selinexor as potential skin sensitiser in the study KNC-G-13-007. The results indicated a mild grade II dermal contact hypersensitivity response at 24 and 48h.

Other toxicity studies

Impurities

The applicant identified the impurities of selinexor, in line with ICH guidance Q3A and S9. In spite that ICH guidance M7 does not apply to drugs intended for advanced cancer indications, the applicant used this guidance to control the genotoxic or potential genotoxic impurities.

Phototoxicity

Selinexor was identified as non-phototoxic in the *in vitro* phototoxicity assay (3T3 fibroblasts using the neutral red uptake assay).

2.3.5. Ecotoxicity/environmental risk assessment

Table 2 Summary of main study results

Substance (INN/Invented Name): Selinexor (KPT-330)			
CAS-number (if available): 1393477-72-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	3.98	Potential PBT (**N**)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.98	**B/not B**
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.00206	μg/L	> 0.01 threshold (**N**)

Selinexor PEC surface water 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.

2.3.6. Discussion on non-clinical aspects

Selinexor is an inhibitor of XPO1. The rationale for inhibiting XPO1 is given from its overexpression observed in a variety of malignancies, including multiple myeloma.

Pharmacology

The non-clinical characterisation of selinexor included both *invitro* and *in-vivo* studies.

The *in-vitro* studies suggest that selinexor acts to inhibit the nuclear export of many proteins, including several tumour suppressor proteins such as p53, resulting in cell cycle arrest and decreased viability. It is hypothesis that selinexor may be selectively cytotoxic to cancer cells only, however, the data supporting this is weak. Given the mechanism of action, i.e. suppression of nuclear export, it is unlikely that this effect is only going to be mediated in cancer cells.

Efficacy in *in vivo* tumour models has been seen as a single agent and in combination with dexamethasone in line with the proposed indication. The only endpoint investigated in these studies

was tumour growth and therefore it is unclear if the effects on tumour growth translate into increased survival. Moreover, there are both concerns with regards to the methodology and the analysis used for one of the pivotal *in vivo* proof of concept studies where tumour appeared to grow larger than permitted by the protocol. The inclusion of such larger tumours in the analysis may have skewed the data in favour of demonstrating significance for the treatments applied. Nevertheless, it is acknowledged the limitations of such xenograft models and their relevance to the clinical situation.

Pharmacokinetics

With respect to the pharmacokinetic and metabolism data, selinexor was partially profiled. The absorption data for selinexor is limited and is primarily based on data generated in the repeat dose toxicity studies. The metabolite pattern appears similar across the nonclinical species and metabolites appear to account for less than 1% of the parent peak plasma in clinical samples with no unique human only metabolites identified. The *in vitro* studies performed for drug interactions have been primarily performed in line with the FDA guidance document and the applicant has been asked to address where these deviate from the EMA ""Guideline on the investigation of drug interactions" (CPMP/EWP/560/95/Rev. 1 Corr. 2**).

With regards to the potential interactions, minimal activation of hepatic and intestinal CYP3A is expected, given the expected local concentrations of selinexor and its poor solubility at high concentrations. CYP induction studies identified a very potent reduction in CYP 3A4 mRNA levels However, it is accepted that no accumulation of selinexor was seen following multiple dosing, which would support the conclusion that the decrease in mRNA has no *in vivo* implications.

As of metabolites, partial information was provided. Therefore, the applicant committed to conduct additional post-authorisation studies to confirm the structure of the metabolites. The Applicant has committed to submit results from a metabolite characterisation study, by Q1 2021 (CHMP Recommendation).

Toxicology

Rats were chosen as the rodent species and cynomolgus monkeys as the non-rodent species. The nonclinical safety studies are broadly in line with ICH S9. Non-clinical safety program revealed a high toxicity of selinexor. Some tissues were mainly affected (reproductive systems, CNS-mediated gastrointestinal system…) and clinical findings reported (food consumption and body weight reduction, mortality). No safety margin could be established for human studies. A similar question was raised with other XPO1 inhibitors, which were discontinued due to significant toxicity observed (inappetence, body weight reduction…).

On the other hand, selinexor showed no effect on genotoxicity. No carcinogenicity study was conducted, and only maternal and embryo-foetal development toxicity were carried out, indicating a NOAEL value at 0.25 mg/Kg/day for rats. No data for a second species were provided. Selinexor was also identified as non-phototoxic and to induce mild-grade II dermal contact sensitivity response at 24 and 48 hours.

Selinexor PEC surface water 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.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical documentation submitted was considered adequate. The relevant information has been included in the SmPC (sections 4.6, 5.1 and 5.3).

The CHMP considers the following measures necessary to address the non-clinical issue:

- An in-vitro metabolite characterisation study that will constitute the identification of selinexor structural metabolites

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant 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

Study No., Acronym, Phase	**Study Design/Key Objectives**	**Population / N**	**Treatment**	**Status (at time of submission)**
Pivotal Study				
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	Patients with penta-refractory MM N = 123	Selinexor 80 mg + dexamethasone 20 mg twice-weekly (Days 1 and 3 for Weeks 1 to 4), 4-week cycles	Ongoing enrolment complete
Part 1 (Supportive analysis)	Secondary: Evaluate efficacy (ORR, DOR, CBR, DCR, PFS, TTP, TTNT, OS; analysed 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 twice-weekly (Days 1 and 3 for Weeks 1 to 3), 4-week cycles	Completed
Supportive Studies; Multiple Myeloma				

Study No., Acronym, Phase	Study Design/Key Objectives	Population / N	Treatment	Status (at time of submission)
KCP-330-001 Phase 1	Open-label, dose-escalation study Evaluate PK, PDn, anti-tumour response, OS, and tolerability of selinexor Determine the RP2D	Patients with RR AML ≥60 years of age who are ineligible for intensive chemotherapy and/or transplantation N = 213	Selinexor: 60 mg fixed dose or 55 mg/m^2 twice-weekly, 4-week cycle PC: One of the following: • BSC including blood product transfusions, antimicrobials, & GF • BSC + low dose AraC • BSC + hypomethylating agent	Completed
KCP-330-009 SADAL Phase 2b	Open-label, multicentre, low- vs. high-dose study Evaluate efficacy (ORR, DOR, DCR) of study treatment Assess safety profile of study treatment	Pts with RR DLBCL N = 220a	Low dose: Selinexor 60 mg, twice-weekly, 4-week cycle High dose: Selinexor 100 mg twice-weekly, 4-week cycle	Ongoing
KCP-330- 010 SIRRT Phase 2	Single-arm, open-label study Determine ORR, DOR, DCR, PFS, OS, QoL Evaluate toxicity of selinexor	Patients with initial or RR RT N = 26	Selinexor 60 mg twice-weekly, 4-week cycle	Completed

AML = acute myeloid leukaemia; AraC = cytosine arabinoside; BSC = best supportive care; CBR = clinical benefit rate; CR = complete response; CRR = complete remission rate; CSR = clinical study report; DCR = disease control rate; DFS = disease-free survival; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; GF = growth factors; ISS = integrated summary of safety; ORR = overall response rate; OS = overall survival; MM = multiple myeloma; PC = physician's choice; PDn = pharmacodynamics; PFS = progression-free survival; PK = pharmacokinetics; Pts = patients; QoD = once every other day; QoL = quality of life; QW = once-weekly; RP2D = recommended phase 2 dose; RR = relapsed refractory; RT = Richter's transformation; TTNT = time to next treatment; TTP = time to progression

2.4.2. Pharmacokinetics

Several bioanalytical methods with a linear range of 1.00-1000.00 ng/mL for determination of selinexor (KCP-330) and its metabolite (KPT-375) in human plasma, human urine and human faeces were validated or qualified and used in the clinical studies. Quantitative analysis of selinexor was

performed by LC-MS/MS. The bioanalytical method validations were subject to QA audit and performed according to local SOPs and procedures.

Noncompartmental analyses were used for the estimation of plasma PK parameters of selinexor and the trans-isomer KPT-375 (where applicable) in the phase 1 studies KCP-330-001, KCP-330-002 and KCP-330-003. In the Phase 2 studies (KCP-330-008, -009, -010) and the pivotal study (KCP-330-012/STORM), sparse PK samples were collected, and a population PK approach was used to estimate the population PK parameters, interpatient variability, covariates and characterisation of the exposure-response analyses. The population PK model was developed using pooled data from 721 patients in seven clinical studies. The model was used to investigate dosing recommendations and any requirement for adjustment in special populations for hepatic and renal impairment and drug interactions. The QT modelling included data for PK time-matched QTc from 85 patients from Studies KCP-330-001 and KCP-330-003.

Absorption

- **Bioavailability**

  The absolute bioavailability has not been conducted in humans. Oral bioavailability of selinexor in mice, rats and monkeys is high. At therapeutic dose of 80 mg (approximately 45 mg/m2), the mean C_{max} was 680 ng/mL (1.5 µM) and $AUC_{0-\infty}$ was 5386 ng*hr/mL.

- **Bioequivalence**

  Following a single, 60 mg, oral dose of selinexor in 3 different formulations to fed male and female patients with advanced sarcoma, the second generation tablet was considered functionally bioequivalent to the first generation tablet with regard to total drug exposure as measured by AUC0-t and $AUC_{0-\infty}$. While C_{max} was slightly outside the 90% CI of 80% to 125% CI criteria, the geometric mean ratio was close to 100% (GMR 103.2%).

- **Influence of food**

  The presence of food (high- or low-fat meals) delayed selinexor absorption (t_{max}) from 1.5 to approximately 2-4 hours with minimal impact on exposures (the geometric mean ratio ranged between 114.7% and 125.5%).

Distribution

Plasma protein binding of selinexor is greater than 95% and is not concentration dependent (KS-0025). The blood to plasma ratio was less than 1, suggesting minimal association with red blood cells (KS-50013). The apparent volume of distribution after oral administration (V/F) ranged from 1.5 to 2.1 L/kg, suggesting that selinexor is distributed into tissues. At the recommended dose of 80 mg (approximately 45 mg/m2), the V/F was 1.8 L/kg.

Elimination

- **Excretion**

  Selinexor has not been studied in definitive radiolabel mass balance study; however, based on cold metabolism assessment and rat [^{14}C]-selinexor study, it is presumed that selinexor is excreted by hepatobiliary route into faeces with minimal excretion into urine. In rats, the major route of excretion was via the faeces with 74.7% faecal elimination of radioactivity occurring

by 168 hours post-dose and 70.6% occurring within the first 48 hours post-dose. Urinary excretion was 16.3% of the recovered activity, with 14.6% excreted within the first 72 hours post-dose.

- **Metabolism**

  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 isomerisation 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.

Dose proportionality and time dependencies

Plasma selinexor exposure was dose proportional across and within the 3 - 85 mg/m2 dose range. Volume of distribution, total clearance, and elimination half-life were all independent of selinexor dose.

Figure 2

Dose Proportionality of individual C_{max} vs Dose Following Oral Administration of 3-85mg/m2 selinexor to patients with Advance or Metastatic Solid Tumour Malignancies

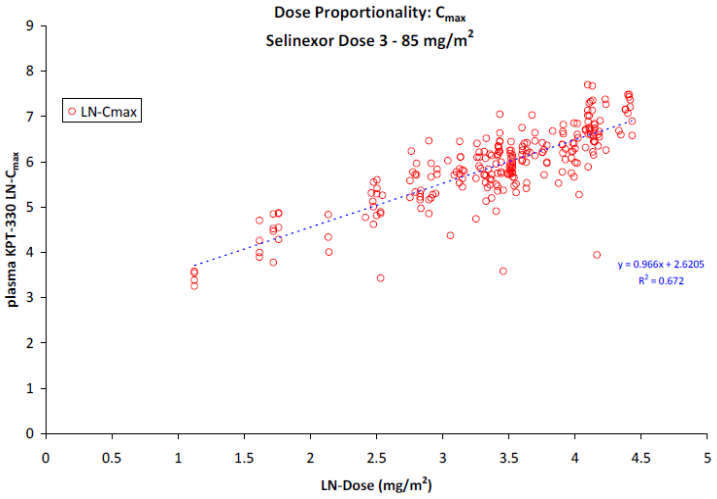
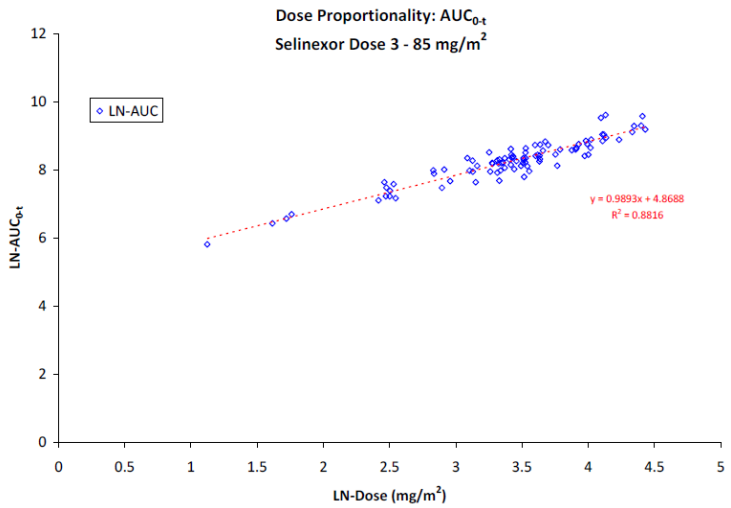


Figure 3 Dose Proportionality of individual AUC_{0-t} vs Dose Following Oral Administration of 3-85mg/m2 selinexor to patients with Advance or Metastatic Solid Tumour Malignancies



In clinical studies, selinexor was dosed as single dose and multiple dose twice or three times weekly and no substantial accumulation (R<1) was evident following repeat dosing. The half-life was 6 hours irrespective of dose and dosing schedule.

Pharmacokinetics in target population

The PPK analysis utilised PK data collected in adult cancer patients (Studies KCP-330-001, KCP-330-002, KCP-330-003, KCP-330-008, KCP-330-009, KCP-330-010, KCP-330-012). For this evaluation the primary purpose was to develop a model that would describe the PK of selinexor in adult cancer patients. A brief summary of the study designs are provided in the Table below:

Table 3 Summary of Clinical Studies Used in Population Pharmacokinetic Analysis

Study [Reference]	Study Population	Study Design	Study Drug Dosage Regimens	# of Subjects with PK	Average Number of PK/ Patient
Study KCP-330-001 [2]	Adult Cancer patients	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	3-80 mg/m^2	131	15.1
Study KCP-330-002 [3]	Adult Cancer patients	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 or Metastatic Solid Tumor Malignancies	3 - 85 mg/m^2	112	15.7
Study KCP-330-003 [4]	Adult Cancer patients	An Open-Label Phase 1B Trial to Evaluate the Effects of Food and Formulation on Pharmacokinetics of the Oral Selective Inhibitor of Nuclear Export/SINE Compound KPT-330 in Patients with Soft-Tissue or Bone Sarcoma	30 mg/m^2 60 mg	37	42.5
Study KCP-330-008 [5]	Adult Cancer patients	SOPRA (Selinexor in Older Patients with Relapsed AML): 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/Refractory Acute Myeloid Leukemia (AML) Who are Ineligible for Intensive Chemotherapy and/or Transplantation	55 mg/m^2 60 mg twice weekly	207	13.4
Study KCP-330-009 [6]	Adult Cancer patients	ADAL: Selinexor Against Diffuse Aggressive Lymphoma: A Phase 2b Open-label Study of Selinexor (KPT-330) in Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma (DLBCL)	60 mg days 1 and 3 of each week Or 100 mg day 1 of each week	194	9.8
Study KCP-330-010 [7]	Adult Cancer	SIRRT Study: Selinexor in Initial or	60 mg twice weekly during	26	9.1

Study [Reference]	Study Population	Study Design	Study Drug Dosage Regimens	# of Subjects with PK	Average Number of PK/ Patient
	patients	Relapsed/Refractory Richter's Transformation A Phase 2 Study of the Safety and Anti-tumor Activity of the Oral Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330) in Patients with Initial or Refractory / Relapsed Richter's Transformation (RT)	Weeks 1-4 of each 4-week cycle		
Study KCP-330-012 [8]	Adult Cancer patients	STORM (Selinexor Treatment of Refractory Myeloma)A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) Plus Low Dose Dexamethasone (Sd) in Patients with Multiple Myeloma Previously Treated with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib, and Daratumumab, and Refractory to Prior Treatment with Glucocorticoids, an Immunomodulatory Agent, a Proteasome Inhibitor, and the anti-CD38 mAb	80 mg plus low-dose dexamethasone (20 mg) (S+D) twice weekly	79	10.1

Source: protocol and final report for Studies KCP-330-001, KCP-330-002, KCP-330-003, KCP-330-008, KCP-330-009, KCP-330-010, KCP-330-012.
mg – milligrams, m - meters, PK - pharmacokinetics

Special populations

- **Impaired renal function**

Robust population PK analyses from patients with normal (N = 261), mild (N = 277), moderate (N = 167) or severe (N = 15) renal impairment (baseline creatine clearance from normal to >15 mL/min) from Phase 1 and 2 studies were conducted. Baseline creatinine clearance had no impact on the PK of selinexor.

- **Impaired hepatic function**

Table 4 Effect of Hepatic Impairment on Clearance of Selinexor

Hepatic Impairment (At Baseline)	Clearance (L/hr)	No. of Patients
Normal	17.7	611
Mild		100
Moderate	15.2	6
Severe		3

In the population PK model, the effect of hepatic impairment was retained and the patients with moderate/severe impairment exhibited 14.1% lower clearance compared to patients with normal liver function or with mild hepatic impairment.

- **Gender**

The clearance value (CL/F) in males was 17.7 L/hr and 14.3 L/hr in females (KS-50040). The AE profile in males and females was generally similar.

- **Race**

The PopPK dataset was categorised for race as White (n=607), Black/African American (n=46), Asian (n=15), or other (n=35). Race was not a significant covariate, suggesting exposures to selinexor were not impacted by race (KS-50040).

- **Weight**

The median body mass index (BMI) in the population PK dataset was 25.8 kg/m2. For the PPK model, BMI was identified as being predictive of CL/F. The patients with lean body mass (13.7 kg/m2) had a lower clearance (76% of clearance [CL] in comparison to CL with median BMI) and obese patients had a higher clearance (38% of CL in comparison to CL with median BMI). The difference in CL due to BMI was not considered clinically relevant as it represents <40% difference.

- **Elderly**

Table 5 Distribution of Geriatric Patients in Clinical Trials Submitted in the MAA

Study	Age 65-74 n (%)	Age 75-84 n (%)	Age 85+ n (%)	% of Subjects Aged 65 and Older / Total
All trials	315 (40.08)	150 (19.08)	15 (1.91)	61.1% / 786
KCP330-001	42 (32.06)	24 (18.32)	3 (2.29)	52.7% / 131
KCP330-002	41 (36.61)	3 (2.68)		39.2% / 112
KCP330-003	9 (24.32)	1 (2.7)		27.0% / 37
KCP330-008	115 (55.56)	70 (33.82)	8 (3.86)	93.2% / 207
KCP330-009	62 (31.96)	44 (22.68)	4 (2.06)	56.7% / 194
KCP330-010	16 (61.54)	4 (15.38)		76.9% / 26
KCP330-012	30 (37.97)	4 (5.06)		43.0% / 79

Pharmacokinetic interaction studies

- ***In vitro***

Effect of Selinexor on the Pharmacokinetics of Other Drugs

The potential for drug interactions due to inhibition of major human CYPs (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5) is low (all IC50s for CYP inhibition >10 μM), including CYP3A4/5 (IC50 of 24 μM). No demonstrable CYP induction by selinexor was observed *in vitro* (KS 50010). Selinexor did not inhibit solute carrier transporters except for marginal inhibition of OATP1B1 and 1B3 (KS 50012). Based on *in vitro* results, selinexor twice-weekly is not expected to alter the exposures of other drugs.

Effect of Other Drugs on the Pharmacokinetics of Selinexor

Selinexor is not a substrate for major transporters BCRP, P-gp, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, or MATE2. The applicant has used the measured IC_{50} values of selinexor for the transporters instead of the inhibition constant (K_i) as recommended in the EMA guidance. However, it is considered justified that Ki values equals IC_{50} for selinexor under the given experimental conditions and that the potential for selinexor to inhibit the tested transporters *in vivo* is unlikely.

In a definitive CYP inhibition study with CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5 (KS-50010; Module 2.6.4) based on FDA's recent guidance on DDIs (FDA Guidance for Industry 2017), the inhibition potential was very low (all IC_{50S} >10 μM), including for CYP3A4/5, where an IC_{50} of 24 μM was observed. These results indicate that no clinically meaningful inhibition of major human CYPs, including CYP3A4/5, would be expected.

- ***In vivo***

Effect of Other Drugs on the Pharmacokinetics of Selinexor

Table 6 Numbers of Patients Taking Concomitant Medications

Drug Type	N	Concomitant Medication
No Con Meds	596	--
CYP3A4 Inhibitors	143	Ciprofloxacin, Clarithromycin, Diltiazem, Fluconazole, Itraconazole, Ketoconazole, Posaconazole, Voraconazole
CYP3A4 Inducers	3	Carbamazepine, Enzalutamide, Phenytoin
CYP2D6 Inhibitors	12	Buproprion, Paroxetine, Terbinafine
CYP2C8 Inhibitors	6	Clopidogrel

Pharmacokinetics using human biomaterials

N/A

2.4.3. Pharmacodynamics

Mechanism of action

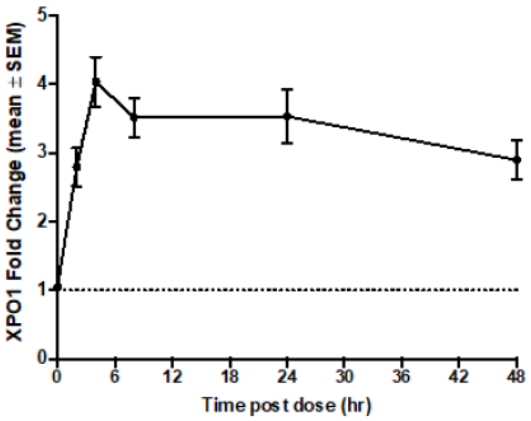
Selinexor is a reversible covalent selective inhibitor of nuclear export (SINE) compound that specifically blocks exportin 1 (XPO1). XPO1 is a nuclear export protein that transports cargo proteins from the nucleus to the cytoplasm. Selinexor is the major mediator of the nuclear export of many cargos protein including tumour suppressor proteins (TSPs), growth regulators and mRNAs of growth promoting (oncogenic) proteins. XPO1 inhibition by selinexor leads to marked accumulation of TSPs in the nucleus, cell cycle arrest, reductions in several oncoproteins such as c-Myc and cyclin D1, and apoptosis of cancer cells.

Primary and Secondary pharmacology

Primary pharmacology

XPO1 mRNA Induction by Tumour Category and Type: Following selinexor treatment, XPO1 mRNA was significantly induced in peripheral blood cells from patients with haematological cancer (Figure below). The Fmax in XPO1 mRNA occurred at approximately 4 hours following the initial selinexor dose and stayed elevated for up to 48 hours. The $t_{1/2}$ for decline in XPO1 mRNA levels is significantly longer than the PK $t_{1/2}$ of selinexor in human plasma (Gounder 2014 Abdul Razak, 2016), perhaps due to covalent inhibition of XPO1 protein.

Figure 14: Mean Induction of XPO1 Expression in Patients with Hematological Cancer Following Oral Dosing of Selinexor on C1D1 in Study KCP-330-001



Source: Table 57,

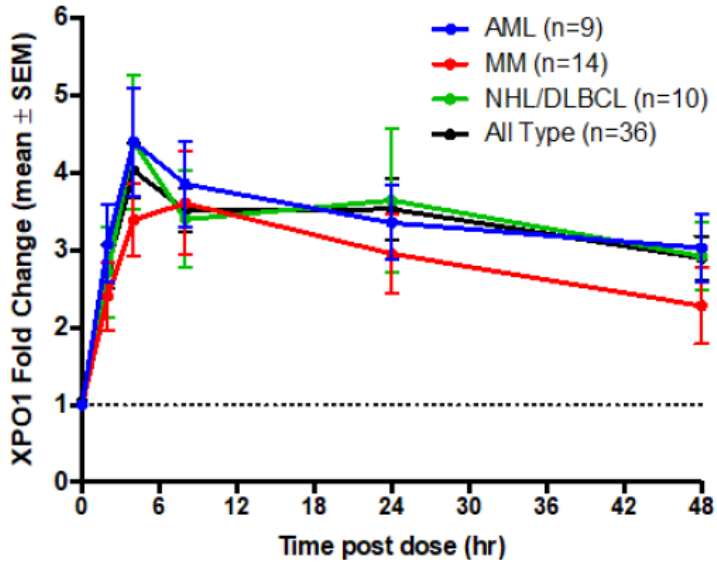
Table 63, Figure 1 of PD Final Report.

C1D1: Cycle 1 Day 1; GAPDH: glyceraldehyde 3-phosphate dehydrogenase; mRNA: messenger ribonucleic acid; PCR: polymerase chain reaction; XPO1: exportin 1 gene/protein.

Note: Fold change in XPO1 mRNA measured in leukocytes isolated from patients (n = 37) enrolled in study KCP-330-001 following a single oral dose of selinexor (3 to 40 mg/m^2). RNA levels were quantitated by qRT-PCR relative to GAPDH internal control and normalized to pre-dose (time 0) mRNA level. The mean fold change from baseline (time 0) versus time post first dose were plotted. XPO1 mRNA was significantly induced relative to baseline (C1D1 pre-dose) levels at post-dose time points ≥2 hours ($p \leq 0.0001$; Analysis of variance with Dunnett's post-test).

To determine whether the magnitude of XPO1 mRNA induction depends on the type of cancer, fold change in XPO1 mRNA was summarised by patient cancer type and plotted against time. The 3 groups of patients were selected based on positive response of these tumour types in the Phase 1 studies and the focus of the later phase clinical studies of selinexor. The magnitude of XPO1 induction remained uniform between different cancer types resulting in almost identical profiles with Fmax between 4 and 8 hours after initial dose of selinexor and consistent up-regulation of >2-fold for up to 48 hours post-dose (Figure below).

Figure 15: Mean Induction of XPO1 Expression in Different Hematological Cancer Subtypes Following Oral Dosing of Selinexor on C1D1 in Study KCP-330-001

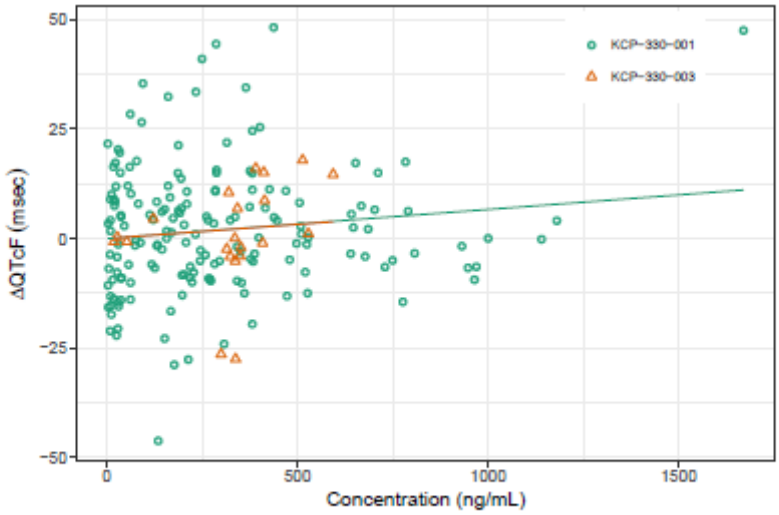


Source: Table 58, Figure 2 of PD Final Report.
AML: acute myeloid leukemia; DLBCL: diffuse large B-cell lymphoma; C1D1: Cycle 1 Day 1; hr: hour; MM: multiple myeloma; NHL: non-Hodgkin lymphoma; SEM: standard error of the mean; XPO1: exportin 1 gene/protein.
Note: Patients with AML (n = 9), NHL/DLBCL (n = 10), and MM (n = 14) were selected from the hematological cancer study. XPO1 fold change values were calculated at each time point (2, 4, 8, 24, and 48 hours after first dose of selinexor).

Secondary pharmacology

Selinexor was anticipated to have a very low potential for QTc interval prolongation on the basis of the *in vitro* assessment of hERG potassium current inhibition. In the *in vivo* cardiovascular assessment in 4-week and 13-week toxicity studies, selinexor showed no AEs in the cardiovascular system in monkeys.

Concentration - QT/QTc analysis: Selinexor inhibited hERG with an IC50 value of 20.6 µM. The IC50 value, based on human plasma protein binding of 95.1% and mean Cmax of 1.53 µM, is estimated to be approximately 250-times higher than the free unbound Cmax of 0.07 µM following an 80-mg dose (KS-0055). A population C-QTc model for selinexor was developed using data from two phase I studies (KCP-330-001 and KCP-330-003). ΔQTcF by time-matched selinexor concentrations are plotted in the figure below.

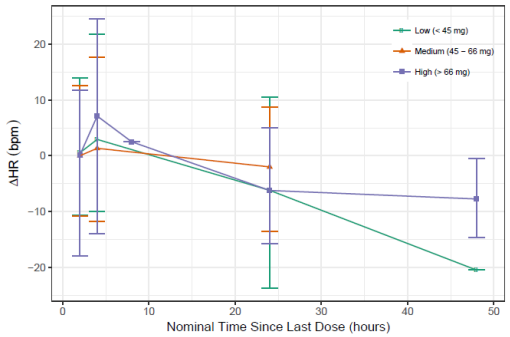


Green circles represent measurements from study KCP-330-001; orange triangles represent measurements from study KCP-330-003; solid lines represent the linear regression for each study.

Selinexor showed a weak positive C-QTc relationship, with the upper bound of the 90% confidence interval of selinexor concentration predicted not to exceed 20 msec ΔQTcF up to 1500 ng/mL (almost 3 times the mean therapeutic concentration). As the mean Cmax selinexor concentration at the intended therapeutic dose of 80 mg (≈ 45 mg/m^2) was 601 ng/mL, based on the model predictions, a clinically relevant QT prolongation is not expected at the recommended therapeutic dose of 80 mg in patients receiving selinexor.

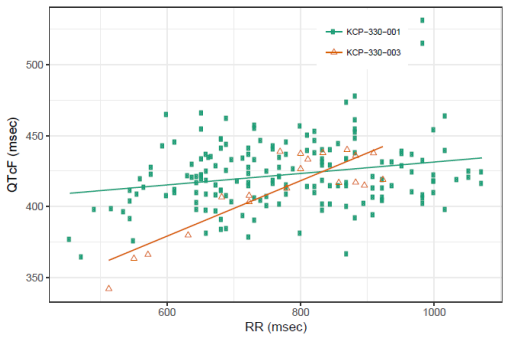
Heart rate: The Heart Rate by time stratified by dose groups is displayed in Figure 5. There appeared to be a trend between Heart Rate and time, however, the confidence intervals overlap, indicating high variability over time. The RR-interval by baseline-corrected QTc interval with Fridericia's correction (ΔQTcF) stratified by study is displayed in Figure 6. There appeared to be study differences in RR-intervals although there were only 6 subjects in study KCP-330-003. There appeared to be a slight trend between ΔQTcF and RR-interval, however, the confidence intervals overlap, indicating high variability for RR-intervals.

Figure 5: Change in Heart Rate by Time



Lines represent the mean value by time. Error bars represent the 5th to 95th percentile range. Note: 1 and 3 observations for the low and high dose group were available at 48 hours post-dose, respectively.

Figure 6: Change in QTcF by RR-interval (Stratified by Study)

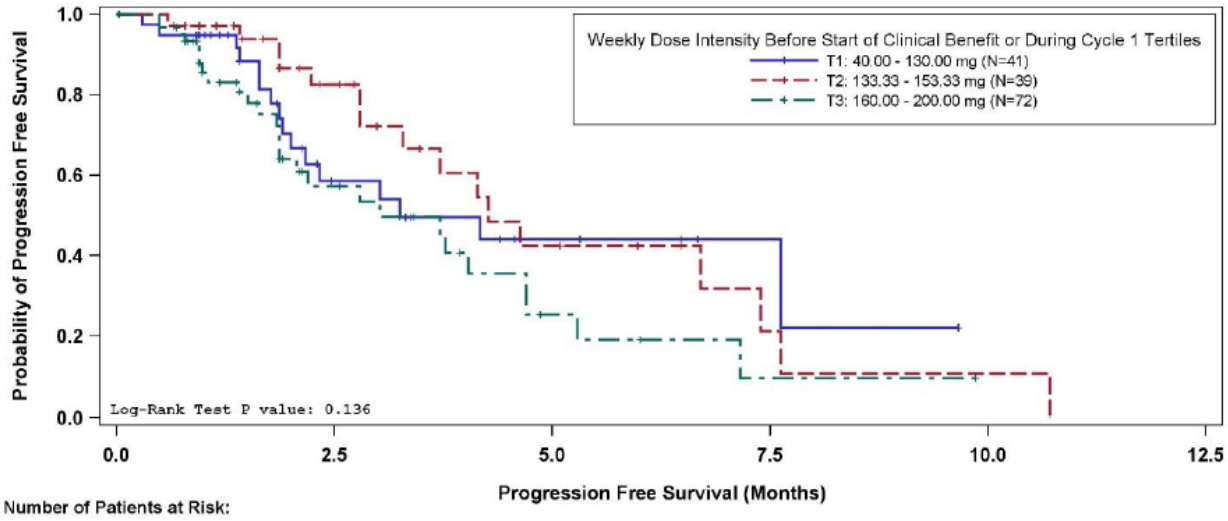


Green circles represent measurements from study KCP-330-001; orange triangles represent measurements from study KCP-330-003; solid lines represent the linear regression for each study.

Relation between plasma concentration and effect

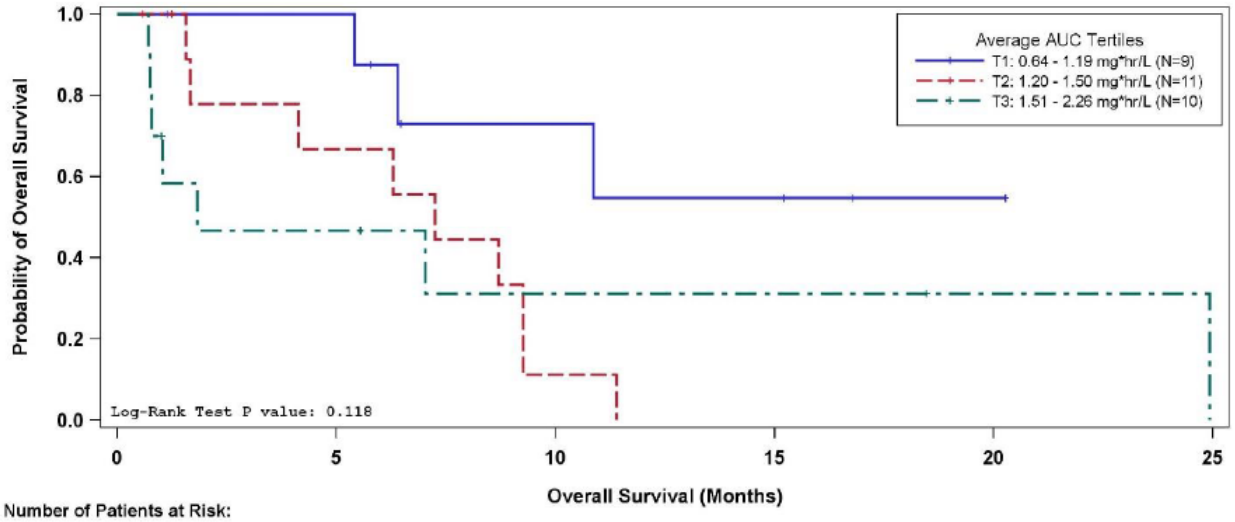
Exposure-efficacy analysis

In the patients with MM treated with selinexor, no significant relationship between BOR, PFS, or OS and AUC or DOSE was observed.



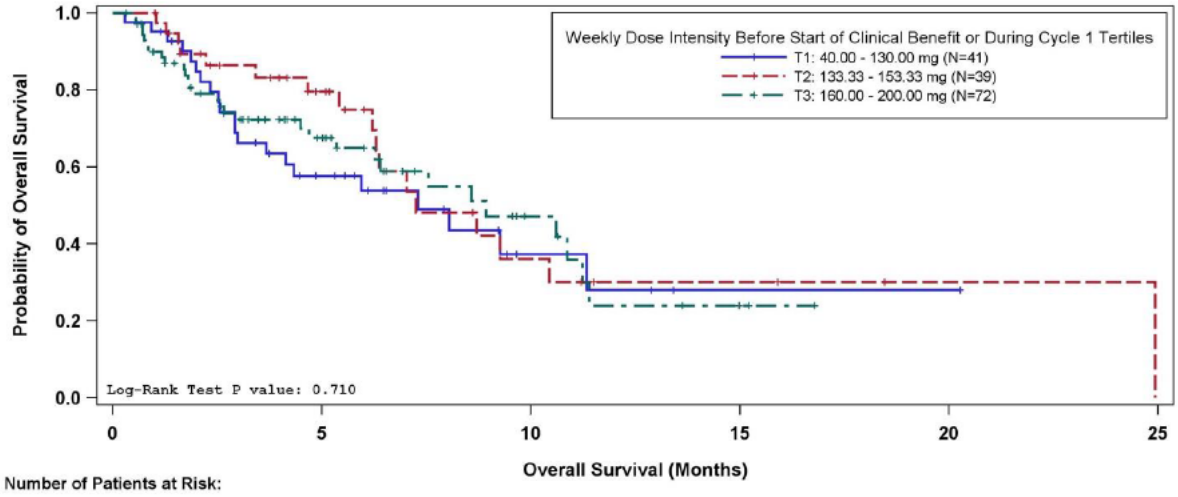
Number of Patients at Risk:

T1:	41	13	6	2	0	
T2:	39	18	7	2	1	0
T3:	72	16	4	1	0	



Number of Patients at Risk:

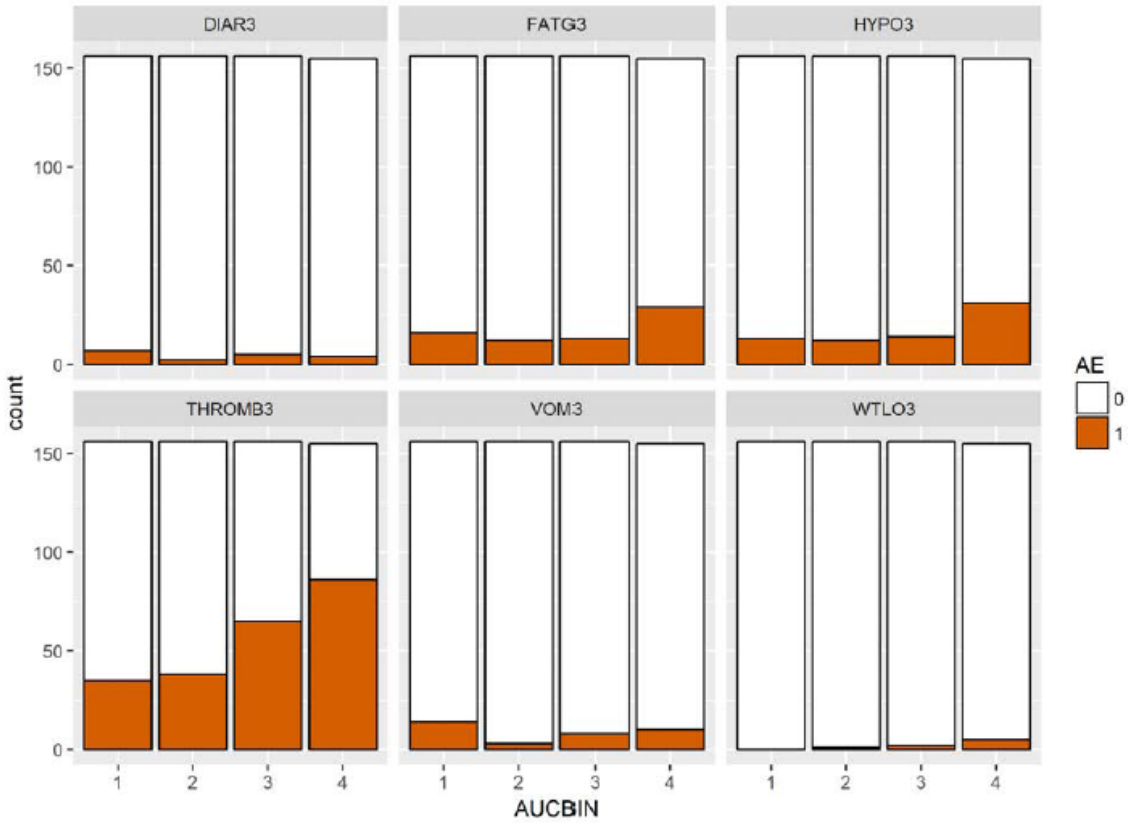
T1:	9	8	4	3	1	0
T2:	11	6	1	0		
T3:	10	4	2	2	1	0

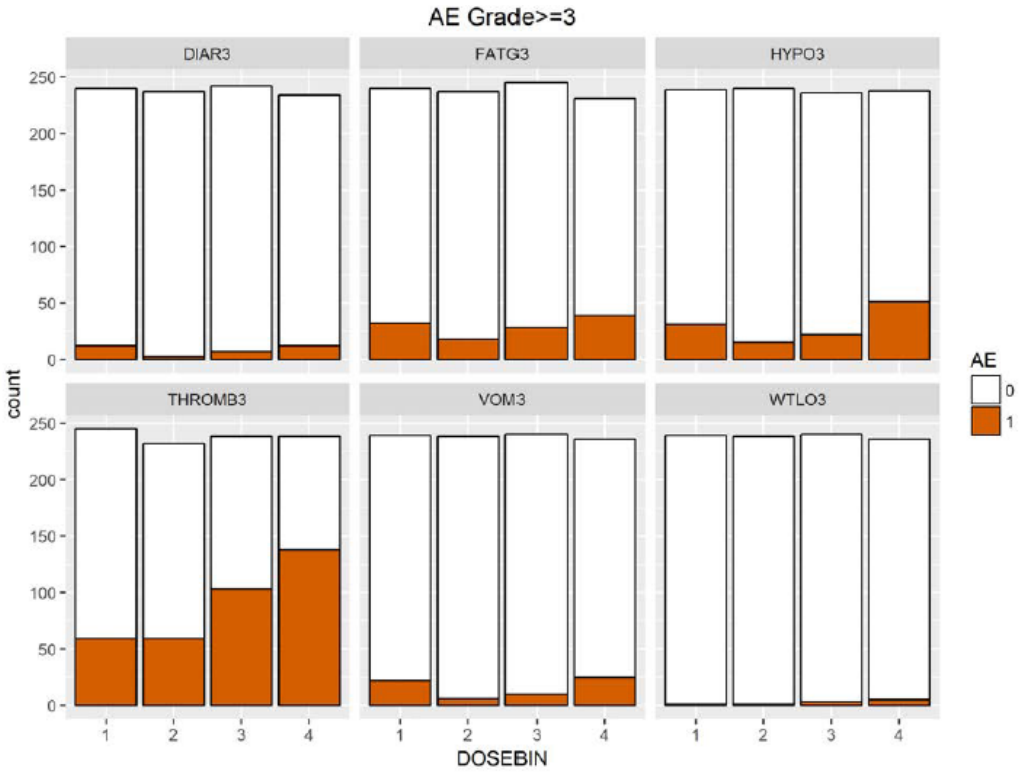


Number of Patients at Risk:

T1:	41	18	4	1	1	0
T2:	39	20	6	3	1	0
T3:	72	28	9	2	0	

Exposure-safety analysis





The analyses highlight thrombocytopenia, hyponatraemia, and fatigue ≥Grade 3 TEAEs as related to selinexor dose (and exposure) and therefore physicians caring for patients on selinexor should actively monitor and aggressively manage these side effects. In contrast, nausea/vomiting, diarrhoea, and decreased weight showed minimal or no association with exposure or dose, although they do occur in the context of selinexor treatment. Although not directly addressed in these analyses, all of the TEAEs considered herein are typically reversible and generally manageable with supportive care.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Selinexor has been characterised using *in vitro* and *in vivo* data from several clinical trials. The methodology applied to characterise the pharmacokinetics and interactions through non-compartmental analysis and population approach is mainly endorsed.

ADME

Selinexor is highly permeable in Caco-2 and MDCKII permeability assays. Selinexor was a weak substrate of BCRP at 0.1 and 1 µM, with efflux ratios of 2.18 and 1.89. BCRP is expected to be saturated even at the lowest 5 mg dose. The solubility at clinically relevant doses and high permeability support that selinexor is primarily absorbed by passive transport and only limited, not clinically relevant, by active transport. The recommended dose is 80 mg (irrespective of BSA and/or body weight). At this dose, the mean C_{max} was 680 ng/mL (1.5 µM) and $AUC_{0-\infty}$ was 5386 ng*hr/mL. The lack of a mass balance study limits to obtain a definitive conclusion about the implication of the metabolites and their main metabolic routes.

The NCA assessment of formulation on the ratios of AUC_{inf} and C_{max} revealed differences between first-generation versus second-generation tablets and fasted versus fed conditions (>±20%). The results

confirmed bioequivalence between TF1 and TF2 for AUC_{0-t} and AUC_{0-inf} but the 90% CI of the geometric mean for Cmax ranged from 87.7 to 130.2, caused by higher variability at C_{max} and the reduced number of individuals enrolled in the study (13 o 14 individuals). The mean of the 90% CI is close to the unity (103), suggesting low influence of tablet formulation on C_{max}.

Metabolism of selinexor occurs through multiple pathways. These include metabolism by CYP3A4, CYP2C9 and various UGTs. Selinexor can also undergo metabolism by GSTs (N-dealkylation, glucuronidation and GSH conjugations) each occurring at <1% of the parent levels. The majority of these metabolites are known to have no XPO1 inhibitory activity. In human faeces, the primary metabolite was KPT-452 (N-dealkylation; inactive metabolite). In human urine, the primary metabolite was KPT-5000 (cystein adduct, inactive metabolite). Selinexor can also undergo racemisation to the trans- form (KPT-375), which is the most common metabolite of selinexor. The KPT-375 isomer has approximately 10% of the XPO1 inhibiting activity of unchanged selinexor and no other known biological properties. The Applicant informs that KPT-375 has mean C_{max} values <5% of those achieved for parent selinexor in all groups. Systemic exposure of KPT-375 is low compared to exposure of selinexor.

The Applicant argues and it is agreed that due to the multiple transformation pathways involved in the elimination of selinexor, it is considered unlikely that PK would be altered in the event of concomitant administrations of modifiers of various enzymes.

Population PK analysis

The population pharmacokinetics of selinexor have been described using a two-compartment model with zero-order release of the drug followed by a first-order absorption, distribution and elimination. Body weight on CL/F and Vc/F and sex on CL/F were identified as statistically significant covariates, which resulted in a more parsimonious model compared to the previous final population PK model. The clinical relevance of body weight and sex on selinexor exposure could be considered of minor relevance (<20% change in AUC), which discards the necessity to establish different dosing recommendations based on patient's characteristics.

Special populations

No dedicated studies for the investigation of special populations have been conducted with selinexor.

Elimination by the renal route is considered minor. Although the number of subjects with severe renal impairment was limited, renal function is considered sufficiently evaluated by population PK analysis, where patients ranging from having normal kidney function to severe renal impairment was enrolled in the clinical phase 1 and 2 studies and thus included in the PPK population. Therefore, mild, moderate, or severe renal impairment is not expected to alter selinexor PK, and no adjustments in the dose of selinexor are required in patients with renal dysfunction (SmPC sections 4.2 and 5.2).

Selinexor undergoes transformation through several hepatic conversion systems but is also able to undergo unchanged excretion. The number of patients studied with moderate or severe hepatic impairment at baseline (N=6 and N=3, respectively) or throughout dosing (N=14 and N=6, respectively) was limited, the impact of hepatic function is nonetheless considered adequately captured by the population PK analysis. This analysis indicated no clinically relevant effect of hepatic impairment between normal and mild hepatic impaired patients. Therefore, no dose adjustment of selinexor is required for patients with mild hepatic impairment There are insufficient data in patients with moderate or severe hepatic impairment to support a dose recommendation (SmPC sections 4.2 and 5.2).

Exploratory analyses of the effect of gender, age and malignancy on PK were conducted. Overall, no indications of clinically relevant PK-altering effects of neither gender, age nor malignancy were found.

The population PK analysis further investigated possible effects. 422 males and 298 females were included in the population PK population. Female patients had significantly lower (19.1%) clearance than male patients, however the effect is not considered clinically relevant. Summary statistics stratified by race were reported. Subjects with Asian origin appear to have slightly higher exposure, and this can be explained by, in general, lower body weight and BSA. Even though the proportion of black subjects is low, exposure appear to be comparable to exposure in white subjects.

In the population PK analysis, a trend towards higher clearance with higher BMI was observed. Clearance would increase about 23% for a subject with a BMI above 40. This effect of BMI on exposure is not considered clinically relevant.

The age range represented in the population PK analysis was wide (18-94 years) with a median age of 68 years. Age was identified as a significant covariate for the absorption rate constant (k_a). However, although younger patients exhibited a lower k_a, the k_a value increased only marginally by 30% in the older age groups. This is not considered clinically relevant. No paediatric patients below the age of 18 were included in the clinical trials contributing PK data.

Interactions

Comparisons of distributions of CL/F, dose normalised AUC, and dose normalised Cmax for patients taking CYP3A4 inhibitors (n=114), CYP3A4 inducers (n=3), CYP2D6 inhibitors (n=12), and CYP2C8 inhibitors (n=4) versus those not taking concomitant medications were also presented as Box-and-Whisker plots and none indicated any clinical relevant drug interaction. The Applicant committed to conduct an *in vivo* DDI study with the potent CYP3A4 inhibitor clarithromycin as a sub-study in STOMP to be completed in Q4 2020.

Selinexor was shown to inhibit CYP3A4/5 and OATP1B1/B3, induce CYP1A2 and was a weak substrate of BCRP *in vitro*. Selinexor has no potential to inhibit hepatic CYP3A (unbound Cmax/Ki = 0.008 after a 100 mg dose which is <0.02) and low potential to inhibit intestinal CYP3A *in vivo* due to limited solubility at pH >3 (Igut/Ki <3). It is considered acceptable that no *in vivo* study investigating CYP4A4/5 inhibition by selinexor is conducted. Results from Study KCP-330-003 indicated that biliary and renal excretion of selinexor is minor. Hence, BCRP is expected to have minimal effect on the absorption of selinexor and no *in vivo* DDI study is required.

Due to limited solubility of selinexor, at the proposed dose level, the expected interaction of selinexor on dexamethasone exposure would be minimal.

Pharmacodynamics

Pharmacodynamic data were primarily derived from study KCP-330-001. All PD data were generated in the target population or in populations with other malignancies. No healthy subjects were included in clinical trials. Selinexor is a reversible covalent selective inhibitor of nuclear export (SINE) compound that specifically blocks exportin 1 (XPO1). The mechanism of action is expected to be shared across various malignancies including the target population of patient with refractory MM.

Primary pharmacology

Changes in XPO1 mRNA were used as a biomarker of PD effects as mRNA transcription increases in response to selinexor inhibition of XPO1 protein function. Selinexor treatment induced a 4-fold increase above baseline of XPO1 mRNA within a period of approximately 4 hours. A dose-dependent relationship is reported. The increase only gradually declined and remained 3-fold increased after 48 hours – which is considerably longer than the selinexor T½ of 6-8 hours. Thus, effects lasting beyond the presence of selinexor are induced. The induction of mRNA by selinexor was consistent across the haematological

cancers investigated which supports that PD results may be extrapolated between patient groups with different haematological malignancies.

Evaluations were performed between selinexor and different efficacy and safety endpoints, suggesting the lack of a significant relationship between selinexor exposure and efficacy outcomes. The exposure-safety analysis revealed thrombocytopenia, hyponatraemia, and fatigue ≥Grade 3 TEAEs as related to selinexor dose and AUC. The Applicant provided the predicted probability of grade >3 fatigue, hyponatraemia and AE's leading to discontinuation across different AUC values (geometric mean, 20% increase and 30% increase). The results suggest a minor effect on all three safety endpoints and the increase of 30% in exposure might not be of clinical relevance.

No patients in the PK population had a ΔQTcF >60 msec, and to date no cases of torsade de pointes or other polymorphic ventricular tachycardia has been reported in patients exposed to selinexor. Although the total number of patients exposed to selinexor is too low to rule out an increased risk of torsade de pointes even though no cases have been observed, the absence of such cases is acknowledged.

Differences in RR-intervals between treatment dose cohorts were observed. The number of patients contributing data was limited and interpretation must be done with caution. Although a slight dose-response relationship was apparent with an increase in heart rate following administration and subsequently declining, the overall changes in heart rate were modest (mean 8 beats per minute increase or decrease, respectively, for the highest dose cohort). A slight trend between ΔQTcF and RR-interval, particularly in study KCP-330-003 was also observed but observations built on data from only 6 patients. In summary, no link between selinexor concentration and increased potential for pro-arrhythmic risk was demonstrated. Further, although a slight increase in heart rate appeared associated with selinexor with an apparent dose-response relationship, the overall changes in heart rate were modest and not considered clinically relevant.

2.4.5. Conclusions on clinical pharmacology

The assessment of the clinical pharmacology properties of selinexor were mostly addressed and characterised using NCA, population PK analysis and exposure-response assessment. The population PK model has been updated, showing the ability of the current structural PK model to properly describe the overall time-course of selinexor.

The overall clinical pharmacology programme can be considered adequate.

The relevant information has been included in the SmPC sections 4.2 and 5.2.

2.5. Clinical efficacy

2.5.1. Dose response study

Study KCP-330-001

Study KCP-330-001 was a Phase 1, open-label, dose escalation study to evaluate the safety and tolerability of oral selinexor and to determine the recommended phase 2 dose (RP2D) —ranging from 3 to 80 mg/m2— in patients with haematologic malignancies (N=285+1) , including RRMM (n= 81).

Study KCP-330-001 was conducted in patients with advanced haematologic malignancies, *including patients with RRMM* with an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0

or 1. Patients with MM must have had symptomatic disease relapsed/refractory to ≥3 prior regimens that included at least an alkylating agent, an IMiD, a PI, and a steroid.

Study KCP-330-001 enrolled 286 patients (1 patient with MM was not treated because of disease progression before dose initiation; total enrolled and treated = 285) with various previously treated haematologic malignancies, 81 of whom had RRMM.

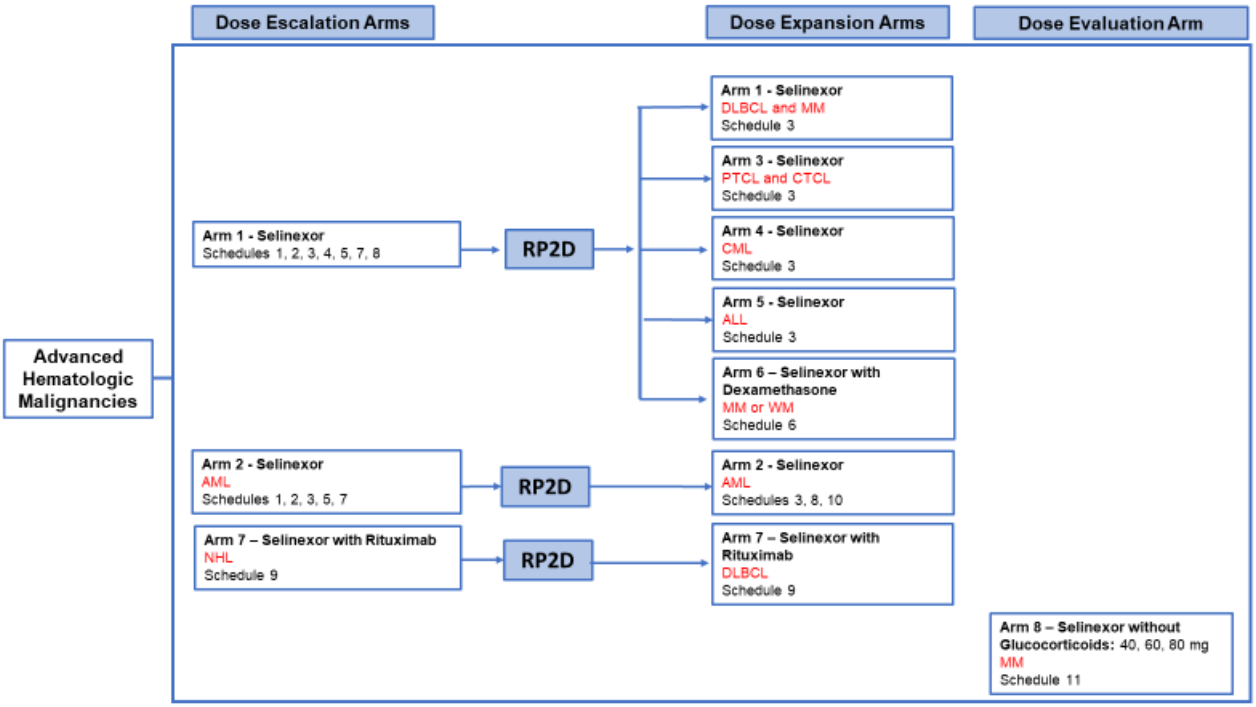
All 81 patients with RRMM have terminated treatment. The most common reason for termination of treatment was PD.

In this study, XPO1 mRNA induction following selinexor dosing reached a maximum at ~4 hours post dose and continued to be elevated at 48 hours post dose. These results indicated a twice-weekly dosing regimen of selinexor would maintain the inhibition of XPO1.

MTD was defined as the next lower dose level below the one in which >1 of 3 patients or ≥2 of 6 patients had a DLT, provided that that dose level was ≤25% lower than the highest (intolerable) dose tested. If the projected MTD was >25% lower than the highest dose tested, then an additional cohort of ≥3 patients was to be added at a dose that was intermediate between the intolerable dose and the next lower dose.

MTD/RP2D was determined independently for each arm in the study, and a dose expansion phase was allowed at either the MTD or the RP2D.

There were 8 arms and 11 schedules divided across 3 types of cohorts.



Several 10-doses-per-cycle, twice-weekly dosing schedules and one once-weekly dosing schedule were explored. Analyses of PK and PDn data from Phase 1 studies ongoing at the time and non-clinical animal data suggested that alternative dosing schedules may be highly active and well tolerated. A standard 3 + 3 design was used for the dose escalation cohorts (Schedules 3 to 9).

All doses described were given orally (PO), once daily (based on corresponding weekly schedule), and with or within 30 minutes of a meal.

Tolerability of selinexor therapy in the absence of GC supportive care was assessed in an ongoing manner by investigators and the sponsor. If the investigator believed that a patient was deriving clinical benefit from selinexor but had difficulty tolerating treatment, and had exhausted available supportive care, that patient received GC supportive care and continued selinexor treatment. However, patients who received GCs in the first 2 cycles were considered not evaluable for Arm 8 single-agent selinexor response, while patients who had completed Cycle 2 without receiving GCs were evaluable for Arm 8 single-agent selinexor response until the date of GC administration.

The recommended phase 2 dose (RP2D) for the KCP-330-001 study was initially determined to be 60 mg/m2. However, further dosing analysis demonstrated that a dose of 35 to 45 mg/m2 had equivalent efficacy and improved long-term tolerability. Hence the RP2D of selinexor as a single-agent for use in this study was selected to be 35 to 45 mg/m2 twice weekly, depending on the indication. The MTD for selinexor has been defined as 70 mg/m2.

The selected dose/RP2D for MM patients was finally 45 mg/m2 selinexor plus 20 mg dexamethasone.

Efficacy results from study KCP-330-001

All Patients with MM

- For all patients with MM (n= 81), the ORR was 8.6% (95% CI: 4, 17) and the CBR was 24.7%, which included 1 patient (1.2%) with an stringent Complete Response (sCR), 6 patients (7.4%) with a Partial Response (PR), and 13 patients (16.0%) with a minimal response (MR). A best response of SD occurred in 29 patients (35.8%). All objective responses in patients with MM occurred at the medium dose range of selinexor.
- Among the 7 patients with MM overall (8.6%) who achieved an objective response, the median DOR was 180 days (95% CI: 57, NC), with the longest response being 518 days.

Table 7 Best Overall Response and Objective Response Rate by Dose Range – All Patients with MM (Efficacy Population)

Parameter	Statistic	Low Dose <30 mg/m^2 (N = 24)	Medium Dose ≥30 mg/m^2 <55 mg/m^2 (N = 39)	High Dose ≥55 mg/m^2 (N = 18)	Total (N = 81)
Best overall response					
Stringent complete response [1]	n (%)	0	1 (2.6)	0	1 (1.2)
Complete response	n (%)	0	0	0	0
Partial response	n (%)	0	6 (15.4)	0	6 (7.4)
Minimal response	n (%)	4 (16.7)	7 (17.9)	2 (11.1)	13 (16.0)
Stable disease	n (%)	9 (37.5)	12 (30.8)	8 (44.4)	29 (35.8)
Progressive disease	n (%)	7 (29.2)	9 (23.1)	4 (22.2)	20 (24.7)
Clinical progression	n (%)	1 (4.2)	0	0	1 (1.2)
Not evaluable/missing	n (%)	3 (12.5)	4 (10.3)	4 (22.2)	11 (13.6)
Objective response rate (ORR) [2]	n (%) 95% CI [3]	0 0.00 - 0.14	7 (17.9) 0.08 - 0.34	0 0.00 - 0.19	7 (8.6) 0.04 - 0.17

*Selinexor **Plus** Dexamethasone 20 mg Twice Weekly*

- For patients with MM treated with selinexor plus dexamethasone overall (dexamethasone administered twice weekly pre-dose [maximum 2 hours before selinexor on dosing days] or at the same time [preferred] as selinexor; n = 25), the ORR was 24% (95% CI: 9, 45) and the

CBR was 32%, which included 1 patient (4.0%) with an sCR, 5 patients (20.0%) with a PR, and 2 patients (8.0%) with a minimal response. Eight patients (32.0%) had SD.

Table 8 Best Overall Response and Objective Response Rate by Dose Range – Patients with MM treated with Selinexor Plus Dexamethasone (Schedule 6) (Efficacy Population)

Parameter	Statistic	Low Dose <30 mg/m² (N = 0)	Medium Dose ≥30 mg/m² <55 mg/m² (N = 12)	High Dose ≥55 mg/m² (N = 13)	Total (N = 25)
Best overall response					
Stringent complete response [1]	n (%)	0	1 (8.3)	0	1 (4.0)
Complete response	n (%)	0	0	0	0
Partial response	n (%)	0	5 (41.7)	0	5 (20.0)
Minor response	n (%)	0	1 (8.3)	1 (7.7)	2 (8.0)
Stable disease	n (%)	0	3 (25.0)	5 (38.5)	8 (32.0)
Progressive disease	n (%)	0	1 (8.3)	4 (30.8)	5 (20.0)
Not evaluable/missing	n (%)	0	1 (8.3)	3 23.1)	4 (16.0)
Objective response rate (ORR) [2]	n (%) 95% CI [3]	0 NC	6 (50.0) 0.21 - 0.79	0 0.00 - 0.25	6 (24.0) 0.09 - 0.45

MM: multiple myeloma; NC: not calculable; ORR: objective response rate.
Note: Overall best response and ORR according to International Myeloma Working Group Response Criteria.
[1] Stringent complete response (sCR) is defined as having a complete response with a normal serum kappa/lambda SFLC ratio.
[2] ORR defined as any response better than a minimal response.
[3] CI = confidence interval, calculated by the exact (Clopper-Pearson) method.

*Selinexor **Without** Dexamethasone 20 mg Twice Weekly*

- For patients with MM treated with selinexor without dexamethasone in the first 2 cycles (n = 11), the ORR was 0 and the CBR was 9% (n=1).

Table 9 Best Overall Response and Objective Response Rate by Dose Range – Patients with MM Treated with Selinexor without Dexamethasone (Schedule 11) (Efficacy Population)

Parameter	Statistic	Low Dose <30 mg/m² (N = 9)	Medium Dose ≥30 mg/m² <55 mg/m² (N = 2)	High Dose ≥55 mg/m² (N = 0)	Total (N = 11)
Best overall response					
Stringent complete response [1]	n (%)	0	0	0	0
Complete response	n (%)	0	0	0	0
Partial response	n (%)	0	0	0	0
Minimal response	n (%)	1 (11.1)	0	0	1 (9.1)
Stable disease	n (%)	3 (33.3)	0	0	3 (27.3)
Progressive disease	n (%)	5 (55.6)	1 (50.0)	0	6 (54.5)
Not evaluable/missing	n (%)	0	1 (50.0)	0	1 (9.1)
Objective response rate (ORR) [2]	n (%) 95% CI [3]	0 0.00 - 0.34	0 0.00 - 0.84	0 NC	0 0.00 - 0.28

MM: multiple myeloma; NC: not calculable; ORR: objective response rate.
Note: Overall best response and ORR according to International Myeloma Working Group Response Criteria.
[1] Stringent complete response (sCR) is defined as having a complete response with a normal serum kappa/lambda SFLC ratio.
[2] ORR defined as any response better than a minimal response.
[3] CI = confidence interval, calculated by the exact (Clopper-Pearson) method.

Selinexor at 45 mg/m2 Plus Dexamethasone 20 mg Twice Weekly

- For patients with MM treated with selinexor at 45 mg/m2 (RP2D) plus dexamethasone (40 mg weekly, n = 12), the ORR was 50.0% (95% CI: 21, 79) and the CBR was 58%, which included 1 patient (8.3%) with an sCR, 5 patients (41.7%) with a PR, and 1 patient (8.3%) with an MR. Three patients (25.0%) had a best response of SD, and 1 patient (8.3%) had PD.
- Among the 6 patients with MM treated with selinexor at 45 mg/m2 plus dexamethasone (50.0%) who achieved an objective response, the median DOR was 180 days (95% CI: 57, NC). These results indicate improvement in the efficacy of selinexor when given with low-dose dexamethasone.

Selinexor at 60 mg/m2 Plus Dexamethasone 20 mg Twice Weekly

- For patients with MM treated with selinexor at 60 mg/m2 plus dexamethasone (40 mg weekly, n = 13), the ORR was 0% and the CBR was 7.7%. One patient (7.7%) had a minimal response. The lack of response observed for 60 mg/m2 selinexor plus dexamethasone 20 mg twice weekly was likely due to poor tolerability of this dose level that resulted in a short time on study for patients.

Table 10 Key Efficacy Results for Patients with RRMM: Study KCP-330-001

Endpoint	All MM N = 81	Single-Agent Selinexor N = 11	Sd[a] N = 25	Sd (RP2D)[b] N = 12
Tumour Response				
ORR[c], n (%)	**7 (8.6)**	0	6 (24.0)	6 (50.0)
95% CI	(4, 17)	(0, 28)	(9, 45)	(21, 79)
CBR[d], n (%)	**20 (24.7)**	1 (9.1)	8 (32.0)	7 (58.3)
Best Response				
sCR/CR, n (%)	1 (1.2)	0	1 (4.0)	1 (8.3)
PR, n (%)	6 (7.4)	0	5 (20.0)	5 (41.7)
MR, n (%)	13 (16.0)	1 (9.1)	2 (8.0)	1 (8.3)
SD, n (%)	29 (35.8)	3 (27.3)	8 (32.0%)	3 (25.0)
PD/NE, n (%)	20 (24.7)	6 (54.5)	5 (20.0)	1 (8.3)
DOR, days; median (95% CI)	180 (57, NC)	NC (NC, NC)	180 (57, NC)[e]	180 (57, NC)
Survival				
PFS, days; median (95% CI)		29 (15, 57)	208 (43, 366)	232 (84, NC)
OS, days; median (95% CI)		174 (38, NC)	NC (103, NC)	NC (103, NC)

Sources: Module 5.3.5.2, KCP-330-001 CSR, Table 14.2.1.3C, Table 14.2.1.2C, Table 14.2.2.3, Table 14.2.4.3, and Table 14.2.5.3, Module 5.3.5.2, KCP-330-001 CSR, Section 11.4.1.3.1.

CBR: clinical benefit rate; CI: confidence interval; CR: complete response; DOR: duration of response; MM: multiple myeloma; MR: minimal response; ORR: overall response rate; NC: not calculable; PD: progressive disease; PFS: progression free survival; PR; partial response; RP2D: recommended Phase 2 dose; RRMM: relapsed/refractory multiple myeloma; sCR, stringent CR; Sd: selinexor in combination with low-dose dexamethasone.

[a] *Sd includes patients who received selinexor 45-60 mg/m^2 plus dexamethasone 20 mg.*

[b] *Selected RP2D (subset of Sd) includes patients who received selinexor 45 mg/m^2 plus dexamethasone 20 mg.*

[c] *ORR = proportion of patients with a confirmed PR or better.*

[d] *CBR = proportion of patients with a confirmed MR or better.*

[e] *The **median DOR** was 180 days (95% CI: 57, NC) in patients treated at 45 mg/m^2 plus 20 mg dexamethasone and **was not calculable in patients treated at 60 mg/m^2 plus 20 mg dexamethasone due to lack of any objective response.***

The most frequently reported adverse events (AEs) included nausea, anorexia, fatigue, thrombocytopenia, and anaemia, which are generally reversible, and can be attenuated with prophylactic and supportive care.

Tolerability was similar between the groups, except for the patients with RRMM treated with the highest dose of selinexor at 60 mg/m2 in combination with dexamethasone (20 mg twice-weekly, n = 13), where the dose was not well tolerated and patients withdrew from the study primarily with constitutional and gastrointestinal symptoms. Overall the most frequently reported adverse events (AEs) included nausea, anorexia, fatigue, thrombocytopenia, and anaemia, which are generally reversible, and can be attenuated with prophylactic and supportive care.

Therefore, based on improved efficacy and similar tolerability, in this Phase 1, dose-escalation study, the RP2D was established at 45 mg/m2 (~80 mg) selinexor in combination with 20 mg dexamethasone, given together twice-weekly. The addition of dexamethasone to selinexor improved outcomes, reported by the applicant as consistent with one of the mechanisms of action of selinexor (i. e. restoration of anti-MM glucocorticoid receptor signalling in the presence of glucocorticoids).

In the subset of patients with RRMM (n=12) who received 45 mg/m2 (~80 mg) selinexor in combination with 20 mg dexamethasone, given together twice-weekly, the ORR was 50% (n= 6) with a median PFS of 232 days; the median OS was not reached. On the basis of these results, this dose was selected as the RP2D and was further evaluated for patients with RRMM in the KCP 330 012/STORM study.

Duration of Response (study KCP-330-001)

Patients without evidence of progression were censored at time of last evaluable disease assessment.

A total of 7 patients with MM (8.6%) achieved an objective response. For all patients with MM, the median DOR was not calculable at the low or high dose ranges and was 180 days (95% CI: 57, NC) at the medium dose range; the longest response in patients with MM was censored at 518 days.

Table 11 DOR for Patients with MM Who Achieved a CR, sCR, or PR

Best Overall Response	Duration of Response
sCR	148
PR	24*
PR	57
PR	79*
PR	310
PR	180
PR	518*

*CR: complete response; DOR: duration of response; MM: multiple myeloma; PR: partial response. Note: Patient 0009-010 achieved a minimal response. * Indicates censored patient.*

Table 12 Time on Therapy Analysis: Comparison Between Selinexor and Most Recent Prior Therapy by Malignancy – MM (Efficacy Population)

Therapy	Parameter	Statistic	MM (N = 81)	P-Value [1]
Selinexor	Time on therapy (days)	75th percentile (95% CI)	80 (59, 113)	0.2752
		Median (95% CI)	36 (29, 46)	
		25th percentile (95% CI)	17 (10, 24)	
	Censored observations	n (%)	0	
	Event rate	n (%)	81 (100.0)	
Most recent prior therapy [2]	Time on therapy (days)	75th percentile (95% CI)	137 (116, 184)	
		Median (95% CI)	89 (53, 102)	
		25th percentile (95% CI)	31 (18, 44)	
	Censored observations	n (%)	0	
	Event rate	n (%)	81 (100.0)	

ID: identification number; MM: multiple myeloma. Note: Time on therapy calculated from the date of start of therapy to the date of end of therapy
[1] P-value is from a stratified log rank test stratified by patient IDs to compare the time on therapy between selinexor and each patient's most recent prior therapy.
[2] Only subjects who received prior therapy are included in the most recent prior therapy analysis.

2.5.2. Main study

Study KCP-330-012/STORM

This was a global, Phase 2b, multicenter, single-arm, 2-part, open-label study designed to evaluate the efficacy and safety of Sd in patients with quad-exposed, double-class-refractory MM (Part 1 only) or penta-exposed, triple-class-refractory MM (Part 1 and Part 2).

Part 1 (supportive analysis) included patients with both quad-exposed, double-class-refractory (lenalidomide, pomalidomide, bortezomib, carfilzomib) (at least 1 PI and 1 IMiD) and penta-exposed, triple-class-refractory MM (quad + refractory and either daratumumab or isatuximab) patients. Two dosing schedules were examined: selinexor 80 mg twice-weekly for 3 weeks of each 4-week cycle and selinexor 80 mg twice weekly continuously in 4-week cycles; dexamethasone 20 mg twice-weekly was given with each dose of selinexor. Results from Part 1 and changes in the treatment landscape contributed to the design of Part 2.

Part 2 (pivotal analysis for this application) included patients with penta-exposed MM, defined as patients who have MM previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab (and an alkylating agent), and triple-class-refractory MM, defined as patients whose disease is refractory to prior treatment with at least 1 IMiD, at least 1 PI, and the anti-CD38 monoclonal antibody (mAb) daratumumab (and glucocorticoids). Patients received selinexor 80 mg in combination with low-dose dexamethasone 20 mg (Sd) twice-weekly on Days 1 and 3 until disease progression, death, or unacceptable toxicity.

Methods

Study Participants

Study KCP-330-012/STORM Part 2: enrolled patients that must have previously received ≥3 anti-MM regimens and have triple-class-refractory MM defined as:

• Previously received lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab and

• Their MM is documented to be refractory to:

- glucocorticoids
- at least 1 IMiD
- at least 1 proteasome inhibitor
- the anti-CD38 mAb daratumumab

Refractory was defined as either **≤**25% response to therapy (≤MR) or progression during or within 60 days after completion of therapy. The patient population included patients with quad-exposed, double-class-refractory and penta-exposed, triple-class-refractory MM in Part 1 and penta-exposed, triple-class-refractory MM in Part 2.

Table 13 Key Inclusion and exclusion criteria in study KCP-330-012/ STORM

Key Inclusion Criteria	Key Exclusion Criteria
Measurable disease based on IMWG guidelines as defined by at least 1 of the following: • Serum M-protein ≥0.5 g/dL by SPEP or quantitative IgA. • Urinary M-protein excretion ≥200 mg/24 hours. • FLC ≥100 mg/L, provided that the FLC ratio is abnormal. Previously received ≥3 anti-MM regimens including: an alkylating agent, lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab, and a glucocorticoid. Refractory to previous anticancer treatments: glucocorticoids, proteasome inhibitor (i.e. bortezomib and/or carfilzomib), IMiD (i.e. lenalidomide and/or pomalidomide), and daratumumab. Refractory: ≤25% response to therapy or progression during or within 60 days after completion of therapy. Refractory to most recent anti-MM regimen. Adequate hepatic function:	Active smouldering MM. Active plasma cell leukaemia. Documented systemic amyloid light chain amyloidosis. Active central nervous system (CNS) MM. Active graft vs host disease (after allogeneic stem cell transplantation) at C1D1. Life expectancy of <4 months. Active, unstable cardiovascular function. HIV seropositive. Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface antigen). Prior malignancy that required treatment or has shown evidence of recurrence (except for non-melanoma skin cancer or adequately treated cervical carcinoma in situ) within 5 years prior to enrolment. Grade ≥3 peripheral neuropathy or Grade ≥2 painful neuropathy. Participation in an investigational anticancer study within 21 days prior to Cycle 1 Day 1.

• Total bilirubin <2 × ULN (Gilbert's syndrome: <3 × ULN) • AST <2.5 × ULN • ALT <2.5 × ULN Adequate renal function • Estimated creatinine clearance of ≥20 mL/min per Cockcroft/Gault Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2 Adequate haematopoietic function • Total WBC count >1000/mm3 • ANC ≥1000/mm3 • Platelet count ≥75,000/mm3 for patients with <50% of bone marrow nucleated cells are plasma cells; or ≥50,000/mm3 for patients with ≥50% of bone marrow nucleated cells are plasma cells. Haemoglobin ≥8.5 g/dL (>8.0 g/dL with approval from medical monitor)	Receipt of transfusions as follows: • Platelet infusion within 1 week prior to Cycle 1 Day 1 • RBC transfusion within 2 weeks prior to Cycle 1 Day 1 Receipt of the following blood growth factors within 2 weeks prior to Cycle 1 Day 1: Granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), erythropoietin (EPO), or megakaryocyte growth factor. Prior exposure to a SINE compound, including selinexor.

Treatments

Patients received selinexor 80 mg PO in combination with low-dose dexamethasone 20 mg (Sd) twice-weekly on Days 1 and 3 until disease progression, death, or unacceptable toxicity.

In selected cases, after 2 cycles of treatment, the selinexor dose may have been increased to 100 mg (<70 mg/m2) twice weekly based on efficacy considerations after a minimum of 2 cycles of study therapy. Dexamethasone 20 mg was administered with each dose of selinexor. For patients with partial intolerance to glucocorticoids (per Investigator), a minimum dose of 10 mg with each dose of selinexor was permitted. In patients with stable disease (SD) or MR who tolerated the treatment, the dose of selinexor could be increased to 100 mg (provided it was <70 mg/m2) after a minimum of 2 cycles of study therapy.

Objectives

Primary Objective:

- To evaluate the efficacy of selinexor 80 mg plus dexamethasone 20 mg (Sd), both dosed PO on Days 1 and 3 weekly in patients with penta-exposed, triple-class-refractory MM enrolled in Part 2 of the study.

Secondary objectives:

- To evaluate the efficacy of Sd in patients with quad-exposed, double-class-refractory and penta-exposed, triple-class-refractory MM in Part 1 of the study

- To determine the safety and tolerability of Sd in patients with RRMM in both parts of the study
- To evaluate the health-related quality-of-life (QoL) of patients with RRMM treated with Sd
- To evaluate the pharmacokinetics (PK) of Sd in patients with RRMM (Part 1 only)

Exploratory objectives:

- To evaluate potential predictive marker of response to Sd in patients with RRMM.

Outcomes/endpoints

Primary endpoint: ORR (overall response rate)

Secondary endpoints:

- DOR (duration of response)
- CBR (clinical benefit rate)
- DCB (Duration of clinical benefit)
- DCR (disease control rate)
- PFS (progression free survival)
- OS (overall survival)
- TTP (time to progression)
- TTNT (time to next treatment)
- QoL (quality of life)

Exploratory endpoint: MRD

Sample size

The sample size for this study addresses the primary study objective of evaluating the clinical effect of Sd in patients with penta-exposed, triple-class-refractory MM by reference to a minimal threshold level for ORR, set to 0.10 (10%). This was based on preliminary evidence from Part 1 of this study, suggesting Sd may exhibit substantial efficacy; therefore, the statistical test associated with the comparison to the threshold will maintain a Type I error rate of 0.025, 1-sided.

For the primary efficacy analysis, a sample size of 122 patients with penta-exposed, triple-class refractory MM will allow a 1-sided test at $\alpha=0.025$ to detect an ORR of ≥ 0.20 against the threshold ORR of 0.10, with 90% power.

Overall, a total of approximately 210 patients was to be enrolled, including:

- Penta-exposed, triple-class-refractory:
  - 122 patients for the primary efficacy analysis (Part 2)
  - 30 patients for supportive efficacy (Part 1)
- Quad-exposed, double-class-refractory: 48 patients for supportive efficacy analyses

Randomisation

Not applicable. This is a single-arm study.

Blinding (masking)

Not applicable. This is an open-label study.

Statistical methods

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

- Screening/baseline visit: occurs within 21 days prior to receiving the 1st dose of study treatment
- Treatment period: expected to be up to 12 months, but there is no maximum treatment duration. Patients will be treated until disease progression, death, toxicity that cannot be managed by standard care, or withdrawal from study, whichever occurs first
- Follow-up period: up to 12 months after last dose of study treatment, patients will be contacted approximately every 3 months for durability of response and survival follow-up.

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

No interim analysis was planned for this study.

Table 14 Efficacy Analysis populations Study KCP-330-012/STORM

Efficacy Populations	Description
Part 2	
Modified Intent-To-Treat (mITT) Population	Patients with penta-exposed, triple-class-refractory MM who met all eligibility criteria and received at least 1 dose of Sd. Includes patients who discontinued therapy due to toxicity or PD or died from any cause. To be used for the primary efficacy analyses.
BCLPD-ref Population (mITT)	Patients in the mITT Population refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab. To be used for supportive efficacy analyses.
CLPD-ref Population (mITT)	Patients in the mITT Population refractory to carfilzomib, lenalidomide, pomalidomide, and daratumumab. To be used for supportive efficacy analyses.
BCPD-ref Population (mITT)	Patients in the mITT Population refractory to bortezomib, carfilzomib, pomalidomide, and daratumumab. To be used for supportive efficacy analyses.
CPD-ref Population (mITT)	Patients in the mITT Population refractory to carfilzomib, pomalidomide, and daratumumab. To be used for supportive efficacy analyses.
Per-protocol (PP) population	All patients in the mITT population with ≥70% compliance to Sd with ≥1 adequate post-baseline response assessment (unless died or withdrew from study prior to first assessment). To be used for supportive efficacy analyses.
High-risk Population (mITT)	Patients with any of the following chromosomal abnormalities: del (17p)/p53, t(14; 16), t(4; 14), and 1q21. To be used for supportive efficacy analyses.
Part 1	
Quad-ref Population	All quad-exposed, double-class-refractory patients who received at least one dose of study treatment. To be used for supportive efficacy analyses.
Penta-ref Population	All penta-exposed, triple-class-refractory patients who received at least one dose of study treatment. To be used for supportive efficacy analyses.
6 Doses per Cycle Population	All quad-exposed, double-class-refractory and penta-exposed, triple-class-refractory patients dosed with Sd twice-weekly for 3 weeks out of each 4-week cycle. To be used for supportive efficacy analyses.

Results

Participant flow

Table 15 Disposition of Patients; Study KCP-330-012/STORM- Flow of the progress

Parameter, n (%)	Part 1 N = 79	Pivotal Part 2 N = 123
Total screened	103	173
Received any dose of study drug	79 (100)	123 (100)
Patients discontinued treatment	79 (100)	123 (100)
Reasons for discontinuation[a]		
Disease progression	45 (57.0)	70 (56.9)
Adverse event	18 (22.8)	39 (31.7)
Patient withdrawal/lost to follow-up	4 (5.1)	5 (4.1)
Investigator decision	11 (13.9)	4 (3.3)
Other	1 (1.3)	5 (4.1)
Patients who have completed 1-year survival follow-up[b]	21 (26.6)	35 (28.5)
Patients who discontinued from the study without completed 1-year survival follow-up	10 (12.7)	14 (11.4)
Patients who died during survival follow-up	44 (55.7)	69 (56.1)

Source: Module 5.3.5.2, KCP-330-012, Table 14.1.1.2.
[a] The denominator for the reasons for discontinuation is the number of patients discontinued.
[b] A patient is considered having completed the 1-year Survival Follow-up if the last Survival Follow-up visit occurred more than 10 months after treatment discontinuation and the patient was alive.
Data cut-off date: 07 September 2019.

Recruitment

The study enrolled patients at 60 sites across 6 countries (Austria, Belgium, France, Germany, Greece and the United States) over the period of 15 months. There was no maximum treatment duration for the study, patients received treatment until progression or intolerability occurred.

Conduct of the study

There were 5 protocol amendments to the KCP-330-012 protocol.

Table 16: Summary of protocol amendments

Amendment Date	Summary of Major Changes
Original 24 December 2014	N/A
Amendment 1 Version 2.0 05 February 2015	Extended the Screening Period from 14 days to 21 days prior to first dose Clarified the roles of the DMC for reviewing safety and response data, the latter added in response to comments by the FDA Added resolution of hematologic toxicities from previous treatments to ≤Grade 2 in response to a deficiency reported by the FDA Modified the skeletal survey to include a central read Clarified that that PFS, QoL, and OS will not be tested for statistical significance, in response to comments from the FDA
Amendment 2 Version 3.0 25 September 2015	Revised the study target patient population from quad-refractory to dual-refractory as shown in the following modified inclusion criteria: From: Patients must have "MM refractory to lenalidomide, pomalidomide, bortezomib, and carfilzomib." To: "Patients must have been previously exposed to lenalidomide, pomalidomide, bortezomib, and carfilzomib" and have "MM double refractory to previous treatment with both the PI and IMiD drug classes" Changed the study treatment (selinexor plus dexamethasone) dose schedule from "twice-weekly for three weeks of every four-week cycle" to "twice-weekly for every week of each four-week cycle." Changed the indication from Multiple myeloma quad-refractory to prior treatment with bortezomib, carfilzomib, lenalidomide, and pomalidomide to Multiple myeloma refractory to prior treatment with an IMiD and a PI. Moved the following objective from exploratory objectives to secondary objectives: "Determine ORR, DOR, PFS, and OS in the subgroup of patients with free light chain (FLC) MM" Added minimal residual disease (MRD) assessment for patients who achieve sCR to Exploratory Objectives Changed the causality assessments From: 1) unrelated, 2) possibly related, or 3) related. To: 1) not related, 2) unlikely related, 3) possibly related, or 4) related. Added a list of the IMWG response criteria
Amendment 3 Version 4.0 11 August 2016	Expanded the population of patients with penta-refractory MM by enrolling approximately 130 additional patients. The overall study population increased to ~210 patients. Revised the study design to make the expansion population (Part 2) the mITT population for the primary efficacy analysis (using ORR); ORR for patients enrolled in Part 1 became a secondary analysis.

Amendment Date	Summary of Major Changes
	Added that the secondary objectives DOR, PFS, DCR, CBR, TTP and OS will be analyzed separately in different patient sub-populations (i.e. Part 1 patients with quad-refractory MM, Part 1 patients with penta-refractory MM, and Part 2 patients with penta-refractory MM). Added that the exploratory endpoints will be analyzed separately for patients with penta-refractory MM and patients with quad-refractory MM. Added the exploratory endpoint "ORR and DOR for Sd vs. the patient's last treatment regimen" and "ORR, DOR, PFS, and OS in patients with International Staging System (ISS) state III vs. ISS stage I or II". Modified inclusion criteria #5 (now #4) to include either daratumumab or isatuximab Modified inclusion criteria #6 (now #5) to include patients with MM refractory to previous treatment with one or more glucocorticoids, parenteral PI (i.e. bortezomib in and/or carfilzomib), IMiD (i.e. lenalidomide and/or pomalidomide), and anti-CD38 mAb (i.e. either daratumumab or isatuximab). Modified inclusion criteria #7 (now #6) (multiple myeloma that is refractory to the patient's most recent anti-MM regimen). The new wording in #6 states that "documented severe intolerance to the patient's last therapy is allowed upon approval by the Medical Monitor." Adjusted inclusion criterion #13 (now #12), requiring adequate platelet count of $\geq$50,000/mm^3 (patients in whom $\geq$50% of bone marrow nucleated cells are plasma cells) at baseline. Added inclusion criteria #13, regarding baseline hemoglobin level $\geq$8.5 g/dL. Deleted exclusion criteria #3, MM that does not express either M-protein of FLC is no longer excluded. Added exclusion criteria #20 and #21, also to require adequate hematopoietic function at baseline. Added exclusion criterion #22, to ensure that patients can tolerate dexamethasone. Established an IRC to perform the central read of response data (for the efficacy analysis) that had been previously included under the Data Safety Monitoring Committee (DSMC) in previous versions of this protocol. The DSMC, now referred to as Data Safety Monitoring Board (DSMB) will retain its role of reviewing all study safety data. Since this study may be pivotal for a regulatory submission, it is important that the involvement of an IRC was readily apparent. Added Canada and the European Union for potential investigatory sites. Added confirmatory review of MM-specific assessments by central laboratory to confirm CR and sCR Changed confirmatory bone marrow sampling from aspirate to core biopsy.

Amendment Date	Summary of Major Changes
Amendment 3.1 Version 4.1 06 February 2017	Removed isatuximab as an allowable anti-CD38 agent for inclusion in the study per the FDA feedback because it was not approved at the time. Corrected exclusion criteria #17 to add ≥before Grade 2 painful neuropathy Modified to require that an IRC confirm disease progression prior to a patient discontinuing study treatment to improve the consistency of clinical decisions across the sites.
Amendment 4 Version 5.0 28 April 2017	Primary purpose for this amendment was to address comments received from Regulatory Authorities. Added the following text, "If any patient is not able to tolerate this dose, then a potential discontinuation or further decrease in dosage would be allowed after a discussion with the Medical Monitor on a case by case basis," to allow for adjustments to the dosing of dexamethasone. Clarify that bone marrow aspirates for MRD analysis are to be collected at response for CR or sCR, not at sCR only. Removed blood draws for PDn and PK analysis as PK and PDn blood samples are no longer being collected. Updated text to reflect IMWG requirement for sequential sample to confirm response, "SPEP with serum protein immunofixation, quantitative Ig, serum FLC, and 24-hour UPEP, with immunofixation, must be collected at each required time point. An aliquot of the blood and urine samples should be retained. If the local laboratory results indicate a CR or sCR, a sequential sample, per IMWG, should be collected and analyzed. Aliquots from the initial and subsequent collection will be sent to the central laboratory to confirm the CR or sCR response." Corrected that karyotyping and FISH will be performed at a central laboratory, not a local laboratory. Pregnancy Testing added, with the following text: "For females of childbearing potential, a negative serum human chorionic gonadotropin (hCG) pregnancy test must be obtained within 3 days before the first dose of study treatment. Test sensitivity for hCG must be ≥25 mIU/mL. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of Cycles ≥2 during the study and at the EoT Visit (serum hCG). Pregnancy testing may also be performed as clinically indicated during the study." Changed volume of Screening bone marrow aspirate from 1x6 mL to 2x10mL to provide sufficient material for PDn tests. Specified that karyotyping and FISH will be performed at a central laboratory
Amendment 5 Version 6.0 13 December 2017	The primary purpose was to update statistical language (e.g. definition of analysis populations, exploratory endpoints) and to address inconsistencies. Objectives: updated for consistency with the Statistical Analysis Plan: Updated definitions of Durations of CBR and DCR

Amendment Date	Summary of Major Changes
	Updated exploratory endpoints Statistical Methods: updated the definition of mITT and PP populations, for consistency with SAP, and removed the presentation of exploratory EE population (details to be provided SAP only) Deleted the following text, as IRC does not review disease assessments at the time of progression and discontinuation of treatment does not require confirmation of PD by IRC: "…and must review at time of progression. Progression based on site generated disease assessment data must be confirmed by the IRC prior to discontinuing treatment." For consistency with Statistical Analysis Plan: updated the definition of mITT and PP populations; removed presentation of exploratory EE population (details to be provided SAP only) Updated Sub-Group Efficacy Analyses

Source: Appendix 16.1.1

Baseline data

Table 17 Patient Demographics; Study KCP-330-012/STORM (Safety Population)

Category	Part 1 N = 79	Pivotal Part 2 N = 123
Age, years; median (range)[a]	63.8 (35, 79)	65.3 (40, 86)
Age category, years; n (%)		
18 – 50	7 (8.9)	8 (6.5)
51 – 64	37 (46.8)	52 (42.3)
65 – 75	31 (39.2)	44 (35.8)
>75	4 (5.1)	19 (15.4)
Gender, n (%)		
Male	37 (46.8)	71 (57.7)
Female	42 (53.2)	52 (42.3)
Race, n (%)		
White	62 (78.5)	86 (69.9)
Black/African American	14 (17.7)	21 (17.1)
Asian	0	2 (1.6)
Native Hawaiian/other Pacific Islander	0	1 (0.8)
Other	2 (2.5)	8 (6.5)
Missing	1 (1.3)	5 (4.1)

Source: Module 5.3.5.2, KCP-330-012, Table 14.1.1.4.
[a] Age is as of the time of the first dose of study drug.
Data cut-off date: 07 September 2019.

Table 18 Disease Characteristics; Study KCP-330-012/STORM, Part 2 (mITT Analysis Population) and Part 1

Characteristic	Part 1 N = 79	Pivotal Part 2 N = 123
Median time from diagnosis to start of study treatment; median (range)	4.88 (0.7, 35.0)	6.58 (1.1, 23.4)
Baseline ECOG performance status; n (%)		
0	15 (19.0)	37 (30.1)
1	49 (62.0)	72 (58.5)
2	9 (11.4)	11 (8.9)
Missing	6 (7.6)	3 (2.4)
Creatinine Clearance at Baseline, n (%)		
<30	4 (5.1)	6 (4.9)
30 to <60	22 (27.8)	34 (27.6)
≥60	53 (67.1)	82 (66.7)
Revised ISS at KCP-330-012/STORM Baseline, n (%)		
I	3 (3.8)	20 (16.3)
II	55 (69.6)	79 (64.2)
III	21 (26.6)	23 (18.7)
Unknown	0	1 (0.8)
High-risk cytogenetics[a] (%)	58 (73.4)	65 (52.8)

ECOG: Eastern Cooperative Oncology Group; ISS: International Staging System; mITT: modified intent-to-treat; n: number of patients.

[a] Results provided for the Safety Population.

Data cut-off date: 07 September 2019

Table 19

Category	Part 2 N=122	Part 1 N=79
Immunoglobulin Type at Baseline, n (%)		
IgG[2]	82 (67.2)	47 (59.5)
IgA[3]	18 (14.8)	19 (24.1)
IgD	0	1 (1.3)
Light chain only	22 (18.0)	9 (11.4)
Light Chain Type at Baseline		
Kappa[4]	80 (65.5)	50 (63.3)
Lambda[5]	42 (34.4)	29 (36.7)
Plasma Cells (%)[6]		
n	107	75
Median	10.5	27.0
Mean (SD)	27.0 (30.67)	37.6 (32.15)
Min, Max	0.0, 95.0	0.0, 97.0
Chromosomal Abnormality, n (%)		
High risk overall[7]	65 (53.3)	58 (73.4)
del(17p)/p53	32 (26.2)	41 (51.9)
del(q13)	25 (20.5)	26 (32.9)
t(4;14)	17 (13.9)	21 (26.6)
t(14;16)	5 (4.1)	6 (7.6)
1q21	40 (32.8)	32 (40.5)

Table 20 Prior Anti-MM Therapy; KCP-330-012/STORM (Safety Population)

Parameter	Part 1 N = 79	Pivotal Part 2 N = 123
Prior treatment regimens, median (range)	7 (2,18)	7 (3, 18)
>5 prior regimens	72 (91.1)	108 (87.8)
≥9 prior regimens	22 (27.8)	36 (29.3)
Duration from most recent systemic therapy to first dose, weeks, weeks; median (range)	4.14 (0.1, 68.6)	4.14 (0.1, 26.0)
Prior exposure to specific individual agents, n (%)		
Lenalidomide		
Previously exposed	79 (100.0)	**123 (100)**
Documented refractory	65 (82.3)	**107 (87.0)**
Pomalidomide		
Previously exposed	79 (100.0)	**123 (100)**
Documented refractory	75 (94.9)	**121 (98.4)**
Bortezomib		
Previously exposed	79 (100.0)	**123 (100)**
Documented refractory	63 (79.7)	**100 (81.3)**
Carfilzomib		
Previously exposed	79 (100.0)	**122 (99.2)**
Documented refractory	76 (96.2)	**119 (96.7)**
Daratumumab		
Previously exposed	21 (26.6)	**123 (100)**
Documented refractory	21 (26.6)	**123 (100)**
Prior stem cell transplant, n (%)	67 (84.8)	102 (82.9)
Documented refractory status, n (%)		
At least 1 IMiD, 1 PI, and daratumumab	20 (25.3)	123 (100)
Triple-refractory (CPD)	19 (24.1)	117 (95.1)
Quad-refractory (CLPD)	16 (20.3)	101 (82.1)
Quad-refractory (BCPD)	15 (19.0)	94 (76.4)
Penta-refractory (BCLPD)	19 (24.1)	83 (67.5)
Additional therapies, n (%)		
Alkylating agent	79 (100)	**123 (100)**
Anthracyclines	39 (49.4)	45 (36.6)
Checkpoint inhibitors	1 (1.3)	19 (15.4)
Glucocorticoid-containing regimens		
1 to 5	31 (39.2)	50 (40.7)
6 to 10	39 (49.4)	64 (52.0)
>10	9 (11.4)	9 (7.3)

Numbers analysed

Data Sets Analysed

Modified Intent-To-Treat Population (mITT) (Part 2): The mITT Population includes all 122 patients with penta-exposed, triple-class-refractory MM treated in Part 2 of the study who received at least 1 dose of either selinexor or dexamethasone.

One patient who received Sd was excluded from the mITT Population because the patient had not received prior carfilzomib.

The mITT Population serves as the primary analysis set for all efficacy endpoints and demographics.

Table 21 Analysis Populations All Patients in Screened Population

	Total (N=208) n (%)
Total Number of Screened Patients	275
Enrolled Total	208 (100.0)
Efficacy Populations	
Modified Intent-to-treat (mITT) [1]	122 (58.7)
Patients With Disease Refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab	83 (68.0)
Patients With Disease Refractory to carfilzomib, lenalidomide, pomalidomide, and daratumumab [2]	101 (82.8)
Patients With Disease Refractory to bortezomib, carfilzomib, pomalidomide, and daratumumab [3]	94 (77.0)
Patients With Disease Refractory to carfilzomib, pomalidomide, and daratumumab [4]	117 (95.9)

(Database Cutoff Date: 2018-04-24) Executed: 2018-07-07

[1] The mITT population consists of Part 2 patients who either met all eligibility criteria or received Sponsor waiver, and received at least one dose of study treatment. The denominator for the other efficacy populations is the number of patients in the mITT population.

[2] Patients may or may not have disease refractory to bortezomib. [3] Patients may or may not have disease refractory to lenalidomide.

[4] Patients may or may not have disease refractory to bortezomib and lenalidomide.

[5] All Penta-refractory Patients consist of the mITT population and the Part 1 penta-refractory patients who either met all eligiblity criteria or receivd Sponsor waiver, and received at least one dose of study treatment.

[6] Part 2 High-risk population consists of patients in the mITT population with any of the chromosomal abnormalities including del (17p)/p53, t(14; 16), t(4; 14), and 1q21.

[7] Part 2 Efficacy Evaluable population consists of patients in the mITT population with at least one adequate, post-baseline IRC-based MM response assessment. [8] Part 2 Per-Protocol populaiton consists of patients in the mITT population without major protocol deviations that are deemed important for statistical analyses.

Additional Efficacy Populations (Part 2): Efficacy was also to be examined by refractoriness to specific previous agents. The following populations are included for primary and secondary efficacy variables and include subsets of the mITT population from Part 2. To be included in a specific subset, documentation of refractoriness to the relevant agent(s) was required.

- BCLPD-ref Population (penta-refractory): The BCLPD-ref Population includes all patients whose MM was documented to be refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab.

The BCLPD-ref Population includes 83 patients.

- CLPD-ref Population: The CLPD-ref Population includes all patients whose MM was documented to be refractory to carfilzomib, lenalidomide, pomalidomide, and daratumumab.

The CLPD-ref Population includes 101 patients.

- BCPD-ref Population: The BCPD-ref Population includes all patients whose MM was documented to be refractory to bortezomib, carfilzomib, pomalidomide, and daratumumab.

The BCPD-ref Population includes 94 patients.

- CPD-ref Population: The CPD-ref Population includes all patients whose MM was documented to be refractory to carfilzomib, pomalidomide, and daratumumab.

The CPD-ref Population includes 117 patients.

Outcomes and estimation

- ***Primary endpoint - Overall Response Rate (ORR)***

Part 2:

The ORR per IRC (mITT Analysis Population) for patients treated in Part 2 was 26.2% (95% CI: 18.7, 35), which included 2 (1.6%) patients with an sCR/CR, 6 (4.9%) patients with a VGPR, and 24 (19.7%) patients with a PR; 16 (13.1%) patients had MR, 48 (39.3%) patients had SD, and 26 (21.3%) patients had PD/NE.

The median time to response of PR or better was 4.1 weeks (range: 1-14).

Part 1:

The ORR per IRC for patients treated in Part 1 was 20.3% (95% CI: 12.0, 30.8), which included 4 (5.1%) patients with VGPR, and 12 (15.2%) patients with a PR; 9 (11.4%) of patients had MR, 30 (38.0%) patients had SD, and 24 (30.4%) patients had PD/NE.

The CBR was 31.6% (95% CI: 21.6, 43.1), which included all patients with an MR or better.

The median time to response of PR or better was 4.1 weeks (range: 2-8).

All Penta-Exposed, Triple-Class-Refractory Patients (Part 2 + Part 1).

For all **penta-exposed, triple-class-refractory patients** treated in both Part 2 and Part 1 (n=152), the ORR per IRC was 25.0% (95% CI: 18.3, 32.7), which included 2 (1.3%) patients with an sCR/CR, 8 (5.3%) patients with a VGPR, and 28 (18.4%) patients with a PR; 22 (14.5%) patients had MR, 54 (35.5) patients had SD, and 38 (25.0%) patients had PD/NE.

Table 22 Overall Response Rate per IMWG as Assessed by the IRC by Prior Anticancer Treatment in Part 2 (mITT Analysis Population)

Subgroup	Part 2 N=122
BCLPD-Refractory, n	83
ORR, n (%)	21 (25.3)
95% CI	16.4, 36.0
CBR, n (%)	31 (37.3)
95% CI	27.0, 48.7

CLPD-Refractory, n	101
ORR, n (%)	26 (25.7)
95% CI	17.6, 35.4
CBR, n (%)	37 (36.6)
95% CI	27.3, 46.8
BCPD-Refractory, n	94
ORR, n (%)	25 (26.6)
95% CI	18.0, 36.7
CBR, n (%)	36 (38.3)
95% CI	28.5, 48.9
CPD-Refractory, n	117
ORR, n (%)	31 (26.5)
95% CI	18.8, 35.5
CBR, n (%)	45 (38.5)
95% CI	29.6, 47.9

Source: Table 14.2.1.1.
B = bortezomib; C = carfilzomib; D = daratumumab; IMWH = International Myeloma Working Group; L= lenalidomide; mITT = modified intent to treat population; P = pomalidomide; CBR = clinical benefit rate; CI = confidence interval; IRC = independent review committee; MR= minimal response; ORR = overall response rate
ORR = proportion of patients with a confirmed PR or better; CBR = proportion of patients with a confirmed MR or better.

Overall Response Rate per IRC by Additional Subgroup Factors

Table 23 Overall Response Rate per IMWG as assessed by the IRC by various subgroup factors for Part 2 (mITT Analysis Population)

Subgroup	Part 2 N=122
Disease Stage / Disease Characteristics	
R-ISS Stage I, n	20
ORR, n (%)	7 (35.0)
95% CI	15.4, 59.2
CBR, n (%)	10 (50.0)
95% CI	27.2, 72.8
R-ISS Stage II, n	78
ORR, n (%)	21 (26.9)
95% CI	17.5, 38.2
CBR, n (%)	32 (41.0)
95% CI	30.0, 52.7
R-ISS Stage III, n	23
ORR, n (%)	4 (17.4)
95% CI	5.0, 38.8
CBR, n (%)	6 (26.1)
95% CI	10.2, 48.4
FLC MM, n	35
ORR, n (%)	15 (42.9)
95% CI	26.3, 60.6
CBR, n (%)	19 (54.3)
95% CI	36.6, 71.2
Non-FLC MM, n	87
ORR, n (%)	17 (19.5)
95% CI	11.8, 29.4
CBR, n (%)	29 (33.3)
95% CI	23.6, 44.3
Cytogenetics	

High-Risk MM, n	65
ORR, n (%)	12 (18.5)
95% CI	9.9, 30.0
CBR, n (%)	24 (36.9)
95% CI	25.3, 49.8
Age	
18-64 years of age	60
ORR, n (%)	16 (26.7)
95% CI	16.1, 39.7
65-74 years of age	44
ORR, n (%)	11 (25.0)
95% CI	13.2, 40.3
≥75 years of age	18
ORR, n (%)	5 (27.8)
95% CI	9.7, 53.5
Region	
US Patients, n	84
ORR, n (%)	26 (31.0)
95% CI	21.3, 42.0
CBR, n (%)	36 (42.9)
95% CI	32.1, 54.1
Non-US Patients, n	38
ORR, n (%)	6 (15.8)
95% CI	6.0, 31.3
CBR, n (%)	12 (31.6)
95% CI	17.5, 48.7

Source: Table 14.2.1.2; Table 14.2.1.6; Table 14.2.1.8; Table 14.2.1.10.
CBR = clinical benefit rate; CI = confidence interval; FLC = free light chain; IRC = independent review committee; mITT = modified intent to treat population; ORR = overall response rate; US = United States; ORR = proportion of patients with a confirmed PR or better; CBR = proportion of patients with a confirmed MR or better.

Overall Response Rate per Investigator Assessment

After the data cut-off of 07 September 2019. For patients in Part 2 (mITT Population) the ORR per investigator assessment was 24.6% and CBR was 34.4%. Best responses included: sCR/CR (n=1; 0.8%), VGPR (n=8; 6.6%), PR (n=21: 17.2%), and MR (n=12; 9.8%).

For patients in Part 1, the ORR per investigator assessment was 20.3% and CBR was 31.6%.

- ***Secondary endpoint - Duration of Response (DOR)***

A key secondary efficacy endpoint for the study was DOR per IMWG as determined by the IRC.

Table 24 DOR for Part 2 (mITT Population) and Part 1

	Part 2 (N = 123)	Part 1 (N = 79)	Total (N = 202)
Duration of Response (Months) - IRC Assessment			
Censored by TTP Rule [1]			
n	32	16	48
Median Duration of Response	4.4	6.2	5.6
95% CI	(3.7, 10.8)	(3.6, 9.8)	(3.7, 10.8)
Patients with Events, n (%)	14 (43.8)	6 (37.5)	20 (41.7)
PD	14 (43.8)	6 (37.5)	20 (41.7)
Death Due to Disease Progression	0	0	0
Patients Censored, n (%)	18 (56.3)	10 (62.5)	28 (58.3)
Death Due to Reasons Other Than Disease Progression	2 (6.3)	0	2 (4.2)
No Adequate Post-Baseline Response Assessment	0	0	0
Documented Treatment Discontinuation and Reasons	16 (50.0)	10 (62.5)	26 (54.2)
Disease Progression per Investigator Assessment	10 (31.3)	3 (18.8)	13 (27.1)
Adverse Event	4 (12.5)	5 (31.3)	9 (18.8)
Physician Decision	0	0	0
Withdrawal by Patient/Lost to follow-up	0	1 (6.3)	1 (2.1)
Other	2 (6.3)	1 (6.3)	3 (6.3)

(Database Cutoff Date: 2019-09-07; Source Data: ADTTE, ADDENOM) Executed: 2019-09-10 9:03
[1] Per TTP rule, duration of response is defined as the duration of first observation of at least partial response to confirmed disease progression or death due to disease progression.
[2] Per PFS rule, duration of response is defined as the duration of first observation of at least partial response to confirmed disease progression or death due to any cause.

NE = not estimable/evaluable/reached

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All Patients with Penta-Exposed, Triple-Class-Refractory MM (Part 1 + Part 2)

Patients with penta-exposed, triple-class refractory MM across both parts of the study: in this population (38 responders), the **median DOR was 5.3 months** (95% CI: 3.7, 10.8.8).

	mITT (Part 2) (N = 122)	All Penta-Ref (N = 152)	Part 2 High-Risk (N = 65)	EE (Part 2) (N = 112)	PP (Part 2) (N = 119)
Duration of Response (Months) - IRC Assessment					
Censored by TTP Rule [1]					
n	32	38	12	32	32
Median Duration of Response	4.4	5.3	3.8	4.4	4.4
95% CI	(3.7, 10.8)	(3.7, 10.8)	(2.3, NE)	(3.7, 10.8)	(3.7, 10.8)
Patients with Events, n (%)	14 (43.8)	18 (47.4)	7 (58.3)	14 (43.8)	14 (43.8)
PD	14 (43.8)	18 (47.4)	7 (58.3)	14 (43.8)	14 (43.8)
Death Due to Disease Progression	0	0	0	0	0
Patients Censored, n (%)	18 (56.3)	20 (52.6)	5 (41.7)	18 (56.3)	18 (56.3)
Death Due to Reasons Other Than Disease Progression	2 (6.3)	2 (5.3)	0	2 (6.3)	2 (6.3)
No Adequate Post-Baseline Response Assessment	0	0	0	0	0
Documented Treatment Discontinuation and Reasons	16 (50.0)	18 (47.4)	5 (41.7)	16 (50.0)	16 (50.0)
Disease Progression per Investigator Assessment	10 (31.3)	11 (28.9)	5 (41.7)	10 (31.3)	10 (31.3)
Adverse Event	4 (12.5)	5 (13.2)	0	4 (12.5)	4 (12.5)
Physician Decision	0	0	0	0	0
Withdrawal by Patient/Lost to follow-up	0	0	0	0	0
Other	2 (6.3)	2 (5.3)	0	2 (6.3)	2 (6.3)

(Database Cutoff Date: 2019-09-07; Source Data: ADTTE, ADDENOM) Executed: 2019-09-10 9:02

[1] Per TTP rule, duration of response is defined as the duration of first observation of at least partial response to confirmed disease progression or death due to disease progression.
[2] Per PFS rule, duration of response is defined as the duration of first observation of at least partial response to confirmed disease progression or death due to any cause. NE = not estimable/evaluable/reached

Table 25 Duration of Response per IMWG Response Criteria as Assessed by the IRC by Previous Anticancer Treatment Part 2 (mITT Analysis Population)

Subgroup	Part 2 N=122
BCLPD-Refractory, n	21
Median DOR (months)	3.8
95% CI	3.7, 10.8
CLPD-Refractory, n	26
Median DOR (months)	3.8
95% CI	2.8, 10.8
BCPD-Refractory, n	25
Median DOR (months)	4.4
95% CI	3.7, 10.8
CPD-Refractory, n	31
Median DOR (months)	4.4
95% CI	3.7, 10.8

Source: Table 14.2.1.14.
B = bortezomib; C = carfilzomib; D = daratumumab; DOR = duration of response; IRC = Independent Review Committee; L= lenalidomide; P = pomalidomide; DOR = duration of response; NE = not estimable
Per TTP rule, duration of response is defined as the duration of first observation of at least partial response to confirmed disease progression or death due to disease progression.

Duration of response was also examined by prior use of daratumumab. The median DOR in patients who had received prior daratumumab as a single agent (± dexamethasone) (n=7) was 2.8 months and 4.4 months in patients who received daratumumab as part of a prior combination therapy (n=25).

In patients who had received daratumumab as their last prior therapy (n=20) the median DOR was 3.8 months and 4.4 months in patients who received daratumumab earlier in their treatment course (n=12).

Median DOR was also examined by prior use of a checkpoint inhibitor. Among the 9 patients who had previously been treated with a checkpoint inhibitor with a response on study, the median DOR was not reached.

Median DOR was also examined by prior SCT. The median DOR was not impacted by prior SCT, with a median DOR not estimable in patients without a prior SCT (n=4), 4.4 months in patients with 1 SCT (n=22), and 3.7 months in patients with >1 SCT (n=6).

Table 26 Duration of Response per IRC by Various Subgroup Factors (mITT Analysis Population) (Part 2 only)

Subgroup	Part 2 N=122
Disease Stage / Disease Characteristics	
R-ISS Stage I, n	7
Median DOR (months)	2.8
95% CI	1.4, 10.8
R-ISS Stage II, n	21
Median DOR (months)	4.4
95% CI	3.8, NE
R-ISS Stage III, n	4
Median DOR (months)	NE
95% CI	3.7, NE
FLC MM, n	15
Median DOR (months)	5.3
95% CI	2.3, 10.8
Non-FLC MM, n	17
Median DOR (months)	4.4
95% CI	2.8, 9.0
Cytogenetics	
High-Risk Patients, n	12

Median DOR (months)	3.8
95% CI	2.3, NE
Age	
18-64 years of age (n)	16
Median DOR (months)	2.8
95% CI	2.1, 4.4
65-74 years of age	11
Median DOR (months)	9.0
95% CI	5.3, 10.8
≥75 years of age	5
Median DOR (months)	NE
95% CI	3.8, NE
Region	
US Patients, n	26
Median DOR (months)	4.4
95% CI	3.7, 10.8
Non-US Patients, n	6
Median DOR (months)	2.8
95% CI	NE, NE

Source: Table 14.2.1.15; Table 14.2.1.19; Table 14.2.1.21.
CI = confidence interval; DOR = duration of response; FLC = free light chain; mITT = modified intent to treat population; IRC = independent review committee; NE = not estimable; US = United States.

- ***Secondary endpoint - Duration of Clinical Benefit (DCB)***

Table 27 Duration of Clinical Benefit per IMWG based on IRC Assessment for Part 2 (mITT Analysis Population) and Part 1 (Safety Analysis Population)

IRC Assessment	Part 2 N=122	Part 1 N=79[a]
Duration of Clinical Benefit (Months) - IRC Assessment, Censored by TTP Rule[b], n	48	25
Median Duration of Clinical Benefit (months)	3.8	5.6
95% CI	3.2, 10.9	4.4, 10.3
Number of Events, n (%)	22 (45.8)	12 (48.0)
Number Censored, n (%)	26 (54.2)	13 (52.0)
Reasons, n %		
Patient Still on Study (database cut)	0	0
Discontinued treatment	22 (45.8)	13 (52.0)
Death (not due to PD)	4 (8.3)	0

Source: Table 14.2.1.23; Table 14.2.1.26.
[a]One patient from Part 1 with penta-exposed, triple refractory myeloma, did not have measurable disease at baseline and thus was excluded from efficacy analysis.
[b]Per TTP rule, duration of clinical benefit is defined as the duration of first observation of at least minimal response to confirmed disease progression or death due to disease progression.
CB = clinical benefit; CI = confidence interval; IRC = independent review committee; NE = not estimable; PD = progressive disease.
Duration of CB was defined as the duration of first observation of at least MR to confirmed PD or death due to PD.

Table 28 Duration of Clinical Benefit per IMWG as Assessed by the IRC by Prior Anticancer Treatment Part 2 (mITT Analysis Population)

Subgroup	Part 2 N=122
BCLPD-Refractory, n	83
Median DCB (months)	3.8
95% CI	2.8, 10.8
CLPD-Refractory, n	101
Median DCB (months)	3.8
95% CI	3.2, 10.9
BCPD-Refractory, n	94
Median DCB (months)	4.4
95% CI	3.7, 10.8
CPD-Refractory, n	117
Median DCB (months)	3.8
95% CI	3.2, 10.9

Source: Table 14.2.1.23
B = bortezomib; C = carfilzomib; D = daratumumab; L= lenalidomide; P = pomalidomide; DCB = duration of clinical benefit; CI = confidence interval; mITT = modified intent to treat population; IMWG = International Myeloma Working Group; IRC = independent review committee; NE = not estimable
Per TTP rule, duration of response is defined as the duration of first observation of at least MR to confirmed PD or death due to PD.

- ***Secondary endpoint - Progression-Free Survival (PFS)***

Table 29 Progression-Free Survival per IMWG based on IRC Assessment or Part 2 (mITT Analysis Population) and Part 1

IRC Assessment	Part 2 N=122	Part 1 N=79[a]
Number of Patients, n	122	79
Median PFS (months)	3.7	4.7
95% CI	2.8, 4.7	3.3, 7.6
Number of Events, n (%)	51 (41.8)	26 (32.9)
Number Censored, n (%)	71 (58.2)	53 (67.1)
Reasons, n %		
No adequate post-baseline assessment	14 (11.5)	11 (13.9)
Patients Still on Study (database cut)	0	0
Discontinued treatment	56 (45.9)	39 (49.4)
Disease Progression per Investigator Assessment	24 (19.7)	19 (24.1)
Adverse Event	21 (17.2)	10 (12.7)
Physician Decision	4 (3.3)	7 (8.9)
Withdrawal by Patient/Lost to follow-up	3 (2.5)	2 (2.5)
Other	4 (3.3)	1 (1.3)
Start of new MM treatment	0	2 (2.5)
Others	1 (0.8)	1 (1.3)

Source: Table 14.2.2.1; 14.2.2.9.
CI = confidence interval; IMWG = International Myeloma Working Group; IRC = independent review committee; mITT = modified intent to treat population; NE = not evaluable.
PFS = progression-free survival
PFS is the duration from start of study treatment to confirmed disease progression or death due to any cause.
[a] One patient from Part 1 with penta-exposed, triple refractory myeloma, did not have measurable disease at baseline and thus was excluded from efficacy analysis.

- ***Secondary endpoint - Time to Progression (TTP)***

Table 30 Time to Progression per IMWG based on IRC Assessment for Part 2 (mITT Analysis Population) and Part 1

IRC Assessment	Part 2 N=122	Part 1 N=79[a]
Median Time to Progression (months)	4.1	5.5
95% CI	3.0, 6.2	3.3, 10.7
Number of Events, n (%)	46 (37.7)	23 (29.1)
Number Censored, n (%)	76 (62.3)	56 (70.9)
Reasons, n %		
Patient Still on Study (database cut)	0	0
Discontinued treatment	56 (45.9)	39 (49.4)
Disease Progression per Investigator Assessment	24 (19.7)	19 (24.1)
Adverse Event	21 (17.2)	10 (12.7)
Physician Decision	4 (3.3)	7 (8.9)
Withdrawal by Patient/Lost to follow-up	3 (2.5)	2 (2.5)
Other	4 (3.3)	1 (1.3)
No Adequate Post-Baseline Response Assessment	14 (11.5)	11 (13.9)
Death (not due to PD)	5 (4.1)	3 (3.8)
Start of new MM treatment	0	2 (2.5)
Others	1 (0.8)	1 (1.3)

Source: Table 14.2.2.2; Table 14.2.2.10.
CI = confidence interval; IMWG = International Myeloma Working Group; IRC = independent review committee; mITT = modified intent to treat population; PD = progressive disease;
Duration of CB is defined as the duration of first observation of at least MR to confirmed PD or death due to PD.
[a] One patient from Part 1 with penta-exposed, triple refractory myeloma, did not have measurable disease at baseline and thus was excluded from efficacy analysis.

Table 31 Time to Progression per IMWG Response Criteria as Assessed by the IRC by Previous Anticancer Treatment Part 2 (mITT Analysis Population)

Subgroup	Part 2 N=122
BCLPD-Refractory, n	83
Median TTP (months)	3.0
95% CI	2.2, 4.7
CLPD-Refractory, n	101
Median TTP (months)	3.7
95% CI	2.8, 4.6
BCPD-Refractory, n	94
Median TTP (months)	3.8
95% CI	2.8, 5.3
CPD-Refractory, n	117
Median TTP (months)	3.8
95% CI	3.0, 5.3

Source: Table 14.2.2.2.
B = bortezomib; C = carfilzomib; D = daratumumab; IMWG = International Myeloma Working Group; L= lenalidomide; mITT = modified intent to treat population; P = pomalidomide; CI = confidence interval; IRC = independent review committee; TTP = time to progression.

- ***Secondary endpoint - Time to Next Treatment (TTNT)***

Table 32 Time to Next Treatment (Prior Therapy vs on-study) for Part 2 (mITT Analysis Population) and Part 1

	Part 2 N=122	Part 1 N=79[a]
Study KCP-330-012		
Median Time to Next Treatment (months)	3.2	2.6
95% CI	2.6, 3.8	1.8, 4.2
Number of Events, n (%)	112 (91.8)	69 (87.3)
New anti-MM therapy	70 (57.4)	53 (67.1)
Death	42 (34.4)	16 (20.3)
Number Censored, n (%)	10 (8.2)	10 (12.7)
Prior treatment to first dose of Sd on Study KCP-330-012		
Median Time to Next Treatment (months)	4.8	3.7
95% CI	3.8, 5.6	3.2, 4.9

Source: Table 14.2.2.3; Table 14.2.2.11.
CI = confidence interval; mITT = modified intent to treat population; MM = multiple myeloma; Sd = selinexor + dexamethasone.
[a] One patient from Part 1 with penta-exposed, triple refractory myeloma, did not have measurable disease at baseline and thus was excluded from efficacy analysis.

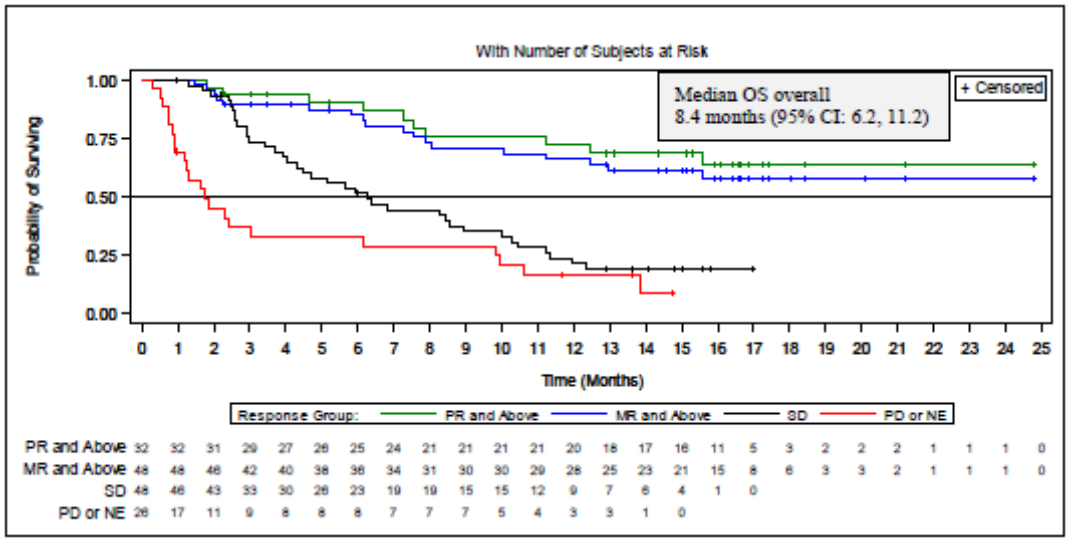
- ***Secondary endpoint – Overall Survival (OS)***

Table 33 OS for Part 2 (mITT Population) and Part 1

	Part 2 N=122	Part 1 N=79[a]
Overall		
Death events, n (%)	76 (62.3)	50 (63.3)
Median OS (months)	8.4	7.3
95% CI	6.2, 11.2	5.8, 10.9
Estimated 6-month survival, %	60.7	60.4
Estimated 12-month survival, %	37.7	33.2
Among Patients with ≥ PR, n	**32**	**16**
Death events, n (%)	10 (31.3)	9 (56.3)
Median OS (months)	NE	12.7
95% CI	15.6, NE	10.3, 24.9
Estimated 6-month survival, %	90.3	85.7
Estimated 12-month survival, %	72.2	50.0
Among Patients with ≥ MR, n	**48**	**25**
Death events, n (%)	18 (37.5)	14 (56.0)
Median OS (months)	NE	11.4
95% CI	12.9, NE	9.3, 24.9
Estimated 6-month survival, %	84.9	87.0
Estimated 12-month survival, %	66.1	45.8
Among Patients with best response of SD, n	**48**	**30**
Death events, n (%)	36 (75.0)	20 (66.7)
Median OS (months)	6.3	6.0
95% CI	4.3, 10.0	4.9, NE
Estimated 6-month survival, %	51.2	50.0
Estimated 12-month survival, %	20.9	40.0
Among Patients with PD or NE, n	**26**	**24**
Death events, n (%)	22 (84.6)	16 (66.7)
Median OS (months)	1.7	3.8
95% CI	1.2, 9.9	1.3, 10.9
Estimated 6-month survival, %	32.6	47.5
Estimated 12-month survival, %	16.3	0.0

Source: Table 14.2.3.1; Table 14.2.3.4.
CI = confidence interval; mITT = modified intent to treat population; MR = minimal response; NE = not estimable/evaluable; PR = partial response; OS = overall survival; PD = progressive disease; SD = stable disease.
Duration of CB is defined as the duration of first observation of at least MR to confirmed PD or death due to PD.
[a] One patient from Part 1 with penta-exposed, triple refractory myeloma, did not have measurable disease at baseline and thus was excluded from efficacy analysis.

Table 34 Kaplan-Meier Estimates for OS Part 2 (mITT Population) by response



Results in the Penta-refractory population

Table 35 Demographics by Analysis Populations penta- refractory BCLPD patients - mITT

	mITT (N = 122)	BCLPD-Ref (N = 83)
Age (Years) [1]		
n	122	83
Median	65.2	65.3
Mean (STD)	64.3 (9.30)	64.5 (9.34)
Min, Max	40 , 86	40 , 86
Age Category [1] n (%)		
18 - 50	8 (6.6)	6 (7.2)
51 - 64	52 (42.6)	34 (41.0)
65 - 74	44 (36.1)	31 (37.3)
>= 75	18 (14.8)	12 (14.5)
Sex n (%)		
Male	71 (58.2)	51 (61.4)
Female	51 (41.8)	32 (38.6)
Race n (%)		
White	85 (69.7)	58 (69.9)
Asian	2 (1.6)	2 (2.4)
Black or African American	21 (17.2)	13 (15.7)
Other	8 (6.6)	6 (7.2)
Native Hawaiian or Other Pacific Islander	1 (0.8)	1 (1.2)
Missing	5 (4.1)	3 (3.6)
Ethnicity n (%)		
Hispanic or Latino	9 (7.4)	7 (8.4)
Not Hispanic or Latino	97 (79.5)	66 (79.5)
Not Reported	15 (12.3)	9 (10.8)
Unknown	1 (0.8)	1 (1.2)

Race n (%)		
White	85 (69.7)	58 (69.9)
Asian	2 (1.6)	2 (2.4)
Black or African American	21 (17.2)	13 (15.7)
Other	8 (6.6)	6 (7.2)
Native Hawaiian or Other Pacific Islander	1 (0.8)	1 (1.2)
Missing	5 (4.1)	3 (3.6)
Ethnicity n (%)		
Hispanic or Latino	9 (7.4)	7 (8.4)
Not Hispanic or Latino	97 (79.5)	66 (79.5)
Not Reported	15 (12.3)	9 (10.8)
Unknown	1 (0.8)	1 (1.2)

Table 36 Baseline Characteristics by Analysis Populations - Modified Intent-to-Treat Population

Characteristic	mITT (N = 122)	BCLPD-Ref (N = 83)
Baseline Height (cm)		
n	122	83
Median	167.5	168.0
Mean (STD)	168.2 (9.76)	168.5 (10.06)
Min, Max	145 , 191	145 , 191
Baseline Weight (kg)		
n	122	83
Median	75.3	75.3
Mean (STD)	77.7 (20.51)	78.4 (17.85)
Min, Max	46 , 208	46 , 132
Body Surface Area (m2) [1]		
n	122	83
Median	1.86	1.87
Mean (STD)	1.88 (0.251)	1.89 (0.230)
Min, Max	1.4 , 3.2	1.4 , 2.5
BMI (kg/m2)		
n	122	83
Median	25.9	26.4
Mean (STD)	27.4 (6.51)	27.6 (5.82)
Min, Max	18 , 64	18 , 50

Baseline ECOG Performance Status n (%) [2]		
0	37 (30.3)	27 (32.5)
1	71 (58.2)	47 (56.6)
2	11 (9.0)	7 (8.4)
Missing	3 (2.5)	2 (2.4)
Duration from Initial Diagnosis (Years)		
n	122	83
Median	6.58	7.05
Mean (STD)	7.24 (4.161)	7.75 (4.470)
Min, Max	1.1 , 23.4	1.2 , 23.4
Response to Most Recent Systemic Therapy n (%)		
Partial Response or Better	53 (43.4)	32 (38.6)
Minimal Response	9 (7.4)	6 (7.2)
Stable Disease	30 (24.6)	20 (24.1)
Disease Progression	17 (13.9)	15 (18.1)
Missing	13 (10.7)	10 (12.0)
Duration of Last MM Treatment (Weeks)		
n	121	82
Median	15.0	11.9
Mean (STD)	19.5 (18.18)	18.0 (16.73)
Min, Max	0 , 93	0 , 93
Time Since Start of Treatment to PD on Last Use of Daratumumab (Weeks)		
Among Patients With Prior Use of Daratumuab in Combination Therapy		
n	84	56
Median	18.1	17.4
Mean (STD)	24.4 (20.87)	23.8 (20.43)
Min, Max	1 , 93	3 , 93
Among Patients Without Prior Use of Daratumuab in Combination Therapy		
n	33	24
Median	12.9	12.6
Mean (STD)	17.3 (15.82)	15.4 (11.45)
Min, Max	4 , 81	4 , 43
Time Since Discontinuation of Last MM Treatment to Start of Study Treatment (Weeks)		
n	122	83
Median	4.14	4.29
Mean (STD)	5.49 (4.088)	5.28 (3.595)
Min, Max	0.1 , 26.0	0.1 , 21.3
Creatinine Clearance at Baseline		
n	121	83
Median	76.9	75.5
Mean (STD)	80.2 (40.96)	78.7 (34.59)
Min, Max	25 , 308	25 , 186

Table 37 Disease History by Analysis Populations - Modified Intent-to-Treat Population

Parameters	mITT (N = 122)	BCLPD-Ref (N = 83)
The International Staging Sytem Stage at Initial Diagnosis, n (%)		
I	20 (16.4)	12 (14.5)
II	23 (18.9)	15 (18.1)
III	38 (31.1)	22 (26.5)
Unknown	41 (33.6)	34 (41.0)
Disease Stage at Diagnosis of Active Myeloma, n (%)		
I	17 (13.9)	11 (13.3)
II	24 (19.7)	16 (19.3)
III	41 (33.6)	23 (27.7)
Unknown	40 (32.8)	33 (39.8)
Current Disease Stage, n (%)		
I	40 (32.8)	25 (30.1)
II	49 (40.2)	34 (41.0)
III	31 (25.4)	23 (27.7)
Unknown	2 (1.6)	1 (1.2)
The Revised International Staging Sytem Stage, n (%)		
I	20 (16.4)	10 (12.0)
II	78 (63.9)	56 (67.5)
III	23 (18.9)	17 (20.5)
Unknown	1 (0.8)	0
B2 Microglobulin Result at Baseline		
n	120	82
Median	3.9	4.0
Mean (STD)	4.7 (3.68)	5.0 (4.23)
Min, Max	0.0, 26.3	0.0, 26.3
Albumin Result at Baseline		
n	121	83
Median	3.7	3.7
Mean (STD)	3.7 (0.47)	3.6 (0.50)
Min, Max	2.3, 4.6	2.3, 4.6

Immunoglobulin Type at Baseline, n (%)		
IgG	77 (63.1)	53 (63.9)
IgA	18 (14.8)	14 (16.9)
IgD	0	0
IgE	0	0
IgM	0	0
Unknown	27 (22.1)	16 (19.3)
Light Chain Type at Baseline		
Kappa	79 (64.8)	53 (63.9)
Lambda	41 (33.6)	29 (34.9)
Unknown	2 (1.6)	1 (1.2)
% Plasma Cells at Baseline		
n	108	74
Median	12.8	17.5
Mean (STD)	27.1 (30.54)	29.4 (30.98)
Min, Max	0.0, 95.0	0.0, 95.0
% Plasma Cells at Baseline, n (%)		
<50	80 (65.6)	54 (65.1)
>=50	28 (23.0)	20 (24.1)
Hemoglobin at Baseline (g/L)		
n	121	83
Median	103.0	101.0
Mean (STD)	105.0 (16.28)	103.7 (15.61)
Min, Max	71.0, 144.0	71.0, 144.0

Table 38 Cytogenetic Overview by Analysis Populations - mITT

	mITT (N = 122) n (%)	BCLPD-Ref (N = 83) n (%)
Patients with High-Risk Chromosomal Abnormality Of		
del (17p)/p53	32 (26.2)	27 (32.5)
t (14;16)	5 (4.1)	4 (4.8)
t (4;14)	17 (13.9)	12 (14.5)
1q21	40 (32.8)	27 (32.5)
Any of del (17p)/p53, t (14, 16), t (4, 14), 1q21	65 (53.3)	47 (56.6)
del 13	25 (20.5)	15 (18.1)

Regarding **efficacy results**, data on ORR and duration of response per IMWG as assessed by the IRC in penta-refractory updated population was 25.3% (95% CI: 16.3, 36) and **median time to first response** 3.9 weeks. Among the 21 responders, 1 had a complete response (CR), 4 had a very good partial response (VGPR), and 16 had a partial response (PR). In addition, 10 patients had a minimal response (MR), 32 had stable disease (SD), and 20 had progressive disease (PD) or were not

evaluable. The reported **median DOR** was 3.8 months (95% CI: 2.3, 10.8). **Median OS** was 8.4 months (95% CI: 5.9; 11.2).

Ancillary analyses

N/A

Summary of main study

The following table summarise the efficacy results from the main study 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 39 Summary of Efficacy for trial KCP-330-012

<table>
<tr><td colspan="4"><u>Title:</u>
Phase 2b, open-label, single-arm study of selinexor (KPT-330) plus low-dose dexamethasone (Sd) in patients with multiple myeloma previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, and immunomodulatory agent, a proteasome inhibitor, and the Anti-CD38 mAb daratumumab<u>.</u></td></tr>
<tr><td>Study identifier</td><td colspan="3">KCP-330-012, EudraCT 2016-003094-18</td></tr>
<tr><td>Design</td><td colspan="3">Phase 2B, open-label, single-arm study to investigate the efficacy of selinexor 80 mg and dexamethasone 20 mg, both twice-weekly in subjects with Multiple Myeloma previously exposed to 5 anti-myeloma agents and refractory to an IMiD, a PI, glucocorticoids and the anti-CD38 mAb daratumumab.</td></tr>
<tr><td></td><td colspan="2">Duration of <u>main phase</u>:

Duration of Run-in phase:
Duration of Extension phase:

Initiation of the study:
Last subject enrolled:</td><td><u>until disease progression, death, or unacceptable toxicity</u>
not applicable
not applicable

26-05-2016
23-03-2018</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Exploratory:
Hypothesis testing will be used for the primary efficacy endpoint data, in order to evaluate if selinexor plus low-dose dexamethasone provides statistically significant improvement in efficacy over a minimally acceptable level of 10% ORR.</td></tr>
<tr><td>Treatments groups</td><td colspan="2">SELINEXOR plus low-dose dexamethasone</td><td>Selinexor 80 mg PO plus low-dose dexamethasone 20 mg PO (Sd) on Days 1 and 3 twice weekly</td></tr>
<tr><td>Endpoints and definitions</td><td>Primary endpoint</td><td>Overall response rate (ORR)</td><td>Proportion of patients who achieved a confirmed partial response (PR) or better (i.e., PR, VGPR, CR, or sCR), as assessed by the IRC, during or after the study treatment, before documented disease progression or initiating a new MM treatment.</td></tr>
</table>

	Secondary endpoint	Duration of response (DOR)	Duration from first response (at least PR) to time of progressive disease (PD) or death due to PD (per IRC), whichever occurred first.
	Secondary endpoint	Overall Survival (OS)	duration from start of study treatment to death from any cause
Database lock	7 September 2019		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Modified Intent-To-Treat (mITT) Population (patients with penta -refractory MM who met all eligibility criteria and received at least 1 dose of Sd. Includes patients who discontinued therapy due to toxicity or PD or died from any cause). 07 September 2019		
Descriptive statistics and estimate variability	Treatment group	**Part-2 PIVOTAL** *Selinexor + dexamethasone*	**Part- 1**
	Number of subjects	N=83	N=79
	ORR, n (%) *(includes sCR + VGPR + PR)* 95% CI	21 (25.3) (16.4,36)	16 (20.3) (12.0,30.8)
	DOR (median, months) 95% CI	**3.8** (2.3, 10.8)	**6.2** (3.6, 9.8)
	OS (median, months) 95% CI	**8.4** (5.9, 11.2)	**8.7** (6.2, 11.3)
	Median TTR	3.9 weeks (range: 1 to 10)	4.1 weeks (range: 2 to 8)
	Discontinuation rate Progression AE	86.2% (106/123) 59/123 (55.7%) 31/123 (29.2%)	100% (79/79) 45/79 (57%) 18/79 (22.8%)

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

N/A

Clinical studies in special populations

	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-330-012	75/202	22/202	1/202
Non Controlled Trials			
KCP-330-001	89/285	43/285	4/285
KCP-330-008	117/213	74/213	8/213
KCP-330-010	16/26	4/26	0/26
KCP-330-013	6/16	5/16	0/16

Supportive studies

The Applicant included the following studies in support of the application:

Study No. Acronym Phase	Study Design/ Key Objectives	Population / N	Treatment	Status
Pivotal Study				
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 + Dex 20 mg twice weekly (Days 1 and 3 for Wks 1-4), 4-wk cycles	Ongoing enrollment complete
Part 1 (Supportive analysis)	Secondary: Evaluate efficacy (ORR, DOR, CBR, DCR, PFS, TTP, TTNT, OS; analysed separately for pts 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 + Dex 20 mg twice weekly (Days 1 and 3 for Wks 1-3), 4-wk cycles	Completed
Supportive Studies; Multiple Myeloma				
KCP-330-001 Phase 1	Open-label, dose-escalation study Evaluate PK, PDn, anti-tumor response, overall survival, and tolerability of selinexor. Determine the RP2D.	Pts with advanced hematological malignancies N=285 (81 pts with MM)	Selinexor: Doses range 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)	Completed

KCP-330-017 STOMP Phase 1b/2	Multicenter, open-label, 2-phase (dose escalation and expansion) study Phase 1: Determine MTD and RP2D and safety and tolerability for each treatment combination Phase 2: Determine efficacy (ORR, DOR, CBR, TTP, PFS, OS) and safety and tolerability for each treatment combination	Pts with ND or RR MM N=117[a]	Selinexor 60 to 100 mg, QW or twice weekly + DEX 20 twice weekly or 40 mg QW Plus 1 of the following: POM 2-4 mg QD BOR 1.3 mg/m^2 QW or twice weekly POM 4 mg QD + BOR 1.3 mg/m^2 QW DARA 16 mg/kg QW CAR 56 or 70 mg/m^2 QW LEN 25 mg QD 28 or 35-day cycles	Ongoing
KCP-330-023 BOSTON Phase 3	Randomized, controlled, open-label 2-arm, active comparator, multicenter study Assess disease response (PFS, ORR, OS, DOR, TTNT, TTR) Compare safety and tolerability and peripheral neuropathy of study treatments	Pts with RR MM N=37[a]	Selinexor 100 mg QW + DEX 20 mg twice weekly (Wks 1-5) + BOR 1.3 mg/m^2 QW (Wks 1-4); 35-day cycles Active comparator: Cycles 1-8: BOR 1.3 mg/m^2 twice weekly + DEX 20 mg 4×weekly (Wks 1-2); 21-day cycles Cycles ≥9: BOR 1.3 mg/m^2 QW + DEX 20 mg twice weekly (Wks 1-4); 35-day cycles	Ongoing
Supportive Studies; Other Hematologic Malignancies				
KCP-330-008 SOPRA Phase 2	Randomized, open-label, active comparator study Determine difference in efficacy (including OS, CRR, CR, DFS, ORR, DCR) and QoL of selinexor vs PC Assess safety and tolerability of selinexor vs PC	Pts with RR AML ≥60 years of age who are ineligible for intensive chemotherapy and/or transplantation N=213	Selinexor: 60 mg-fixed dose or 55 mg/m^2 twice weekly, 4-wk cycle PC: One of the following: • BSC including blood product transfusions, antimicrobials, & GF • BSC + low dose AraC • BSC + hypomethylating agent	Completed

Study No. Acronym Phase	Study Design/ Key Objectives	Population / N	Treatment	Status
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=220[a]	Low dose: Selinexor 60 mg, twice weekly, 4-wk cycle High dose: Selinexor 100 mg twice weekly, 4-wk cycle	Ongoing
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 twice weekly, 4-wk cycle	Completed
KCP-330-013 Phase 2	Multicenter, open-label study Evaluate efficacy (ORR, DOR, DCR, PFS, OS, TTP) Characterize tolerability and safety	Pts with RR PTCL or CTCL N=16	Selinexor 60 mg twice weekly, 4-wk cycles	Completed
Supportive Studies; Solid Tumors				
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, twice weekly or QoD×3 (Wks 1 and 3) and twice weekly (Wks 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 twice weekly 3 different formulations: capsules, tablets (both first and second generation), and a liquid suspension (3 mg/mL) 4-wk cycles	Completed

[220a] Number of patients who received at least 1 dose of selinexor as of 24 April 2018.

AML=acute myeloid leukaemia; AraC=cytosine arabinoside; BOR=bortezomib; BSC=best supportive care; CAR=carfilzomib; CBR=clinical benefit rate; CRR=complete remission rate; CSR=clinical study report; CTCL=cutaneous T-cell lymphoma; DARA=daratumumab; DCR=disease control rate; DEX=dexamethasone; DFS=disease-free survival; DLBCL=diffuse large B-cell lymphoma; DOR=duration of response; GF=growth factors; ISS=integrated summary of safety; LEN=lenalidomide; MTD=maximal tolerated dose; ND=newly diagnosed; OS=overall survival; POM=pomalidomide; PC=physician's choice; PDn=pharmacodynamics; PFS=progression-free survival; PK=pharmacokinetics; PTCL=peripheral T-cell lymphoma; Pts=patients; QD=once daily; QoD=once every other day; QoL=quality of life; QW=once weekly; RP2D=recommended phase 2 dose; RR=relapsed refractory; RT=Richter's transformation; TTNT=time to next treatment; TTP=time to progression; TTR=time to response.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The KCP-330-012/STORM study was a Phase 2b, multicentre, single-arm, 2–part, open-label study designed to evaluate the efficacy and safety of Sd in patients with quad-exposed, double-class refractory MM (Part 1 only) or patients with penta-exposed, triple-class refractory MM (Part 1 and Part 2). Part 2 is the pivotal study for this application.

The population of patients enrolled in both parts of the study has a median age ~64 years, and represents patients with multi-refractory MM who have been treated with several anti MM agents, including a group of patients with RRMM who have received ≥ 9 prior treatment regimens that represents a 30% of the cases.

A main limitation of the study design is the lack of knowledge about the contribution of the mono-components and therefore it is not possible to isolate the treatment effect of selinexor vs. dexamethasone. Additionally, when it comes to contextualising the clinical value of this combination, due to single arm trial design, data especially in these kind of patients with high refractory diseases and where historical data are not fully comparable, are difficult to interpret. The Applicant argues that the inclusion criteria for STORM required patients to have MM that were refractory to glucocorticoids and at least 1 IMiD, at least 1 PI, daratumumab, and their most recent therapeutic regimen. As such, the estimated activity of low-dose dexamethasone in this population was estimated to be negligible (due to the disease being refractory to glucocorticoids). But additionally, it has been argued that selinexor enhances the transcription and translation of the glucocorticoid receptor (GR), thereby increasing GR levels overall. Dexamethasone then activates the GR including enhance its nuclear localisation (required for GR transcriptional activity), leading to a synergistic enhancement of the antitumour transcriptional activity and cell death. That laid into question whether a higher dose of corticosteroids would be associated with an improved effect and it is questionable that the ORR observed in patients receiving Sd therapy is reflective of the activity of selinexor when selinexor activity as monotherapy do not show good outcomes.

The primary endpoint is ORR in patients with penta-exposed MM whose disease is triple-class-refractory to prior therapies. The primary analysis of ORR was designed to determine the superiority of Sd to the minimal threshold for ORR.

The initial design of the study for Part 2 was defined as a threshold of 10% for ORR (using a 2-sided, exact 95% CI and calculated for the rate of ORR among the mITT population) to meet the primary endpoint. The primary endpoint is acceptable in SAT for regulatory purpose where there is no alternative therapy with proven benefit in terms of PFS or OS, since this is a clear reflection of the pharmacodynamic effect (antitumour activity).

An Independent review committee (IRC) was set up to assess the best overall response (primary efficacy endpoint: ORR). However, for the assessment of the ORR, patients with "unconfirmed response" have been taken into account as exploratory analysis, possibly due to lack of relevant data in some subjects, to assess the response category. Amendment 4 was carried out throughout the study, involving this requirement of a confirmatory sequential sample (blood sample and/or urine sample, as appropriate) to confirm response-categories (PR, VGPR, CR or sCR) as it is demanded per current IMWG criteria, therefore previous assessments of response of patients involved in the study until the amendment 4 was applied, could be affected by this issue, which is a matter of concern. This point seems to affect critical aspects, as the assessments of MP in urine samples, in some cases have not been processed. It is well known that sFLC are of clinical value for monitoring disease, but they are not accepted as interchangeable for urine assessments in the current criteria. It is acknowledged that sFLC do not reflect perfectly the quantification of urine MP and for now it is required for response assessment. Additionally, other critical points for response assessment as stated in the current IMWG criteria have not been strictly followed, which eventually could overestimate the reported ORR.

Globally the definition of analysis populations is supported, although the mITT was used for the efficacy analyses: the difference between the ITT and the mITT was only one patient, who was excluded because the patient did not receive prior carfilzomib. While the exclusion of one patient would not change the overall response results, the efficacy results using the ITT population instead of mITT has been reported in the SmPC, including all subjects that were treated with Sd.

Efficacy data and additional analyses

On analysing firstly the information from dose – finding / supportive studies, it is noted that in the selected Sd-RP2D population (cohort 6) of study **KCP-330-001** the patients with better outcomes were those who received selinexor 45 mg/m2 plus dexamethasone 20 mg twice weekly. Although the rate of response to Sd is reasonably high in the selected RP2D, which consists of patients of very poor prognosis and with few therapeutic alternatives, this population is very small (n=12) and the data with higher doses, i.e. selinexor 60 mg/m^2 plus dexamethasone 20 mg twice weekly, which was the initially determined RP2D, (n=13) showed a significant toxicity that leads to the early withdrawal of treatment.

In addition, it draws attention to the lack of objective responses in the population of selinexor as single agent in the **KCP-330-001 study**. Therefore, the addition of dexamethasone is reasonable as corticosteroids are usually administered as backbone therapy and additionally due to the potential synergistic benefit for better responses.

Patients in the pivotal study **KCP-330-012/STORM** had received more previous treatments than those in previous registration studies, which points to a more refractory disease and more immunosuppressed patients with a worse general condition than in previous studies.

Response assessment was performed following the last IMWG response criteria (Kumar 2016). Following these criteria all response categories require two consecutive assessments made any time before starting any new therapy. As previously noted, the primary analysis of ORR was designed to determine the superiority of Sd to the minimal threshold for ORR, documentation of response required two consecutive readings of the applicable disease parameter (serum M-protein (sMP), urine M-protein (uMP), serum FLC (sFLC), or quantitative immunoglobulin level). As reported by the MAH the confirmatory response assessment may have been obtained the same day as the initial response assessment but must have been analysed separately, since an unconfirmed response may be associated with the patient's specific situation and it could not reflect the real response of the disease or it could be distorted by a technical error. This fact is even more relevant in cases where the disease is within the limits of detection of the technique applied (e.g. RC). This means that it does not represent a true stability of the response, but a punctual response, which can magnify the actual ORR. ORR was also assessed based on investigator assessment of response.

In the same line, patients with uMP at baseline, without follow up in uMP and/or confirmation of response in uMP, cannot be evaluated. Serum FLC levels should only be used for response assessment when both the serum and urine M-component levels are deemed not measurable. This implies that it cannot systematically replace a mandatory evaluation of uMP according to the current criteria. Accordingly, and given the fact that we are faced with a single-arm study, without comparator and with ORR as a primary efficacy assessment endpoint, the application of response criteria by IMGW must be highly strict in order to assess the actual efficacy of the new drug. Subtle changes in the application of the response criteria could overestimate the actual value of the ORR.

Therefore, and with all these doubts in mind, a systematic review was performed of all patients where a response rate was achieved according to the CSR. Based on this, the company’s statement of at least a PR in all 32 patients considered as responders, was not supported. Further, in the context of the critical issues identified during the routine GCP inspection conducted in March 2019 the applicant undertook a re-monitoring of ‘all responders’ (i.e. 32 patients) in the study. An update on 9 patients in which the re-monitoring exercise identified data edits, as well as additional justification to support the 10 responses under discussion were submitted. The identified previous doubts in 10 patients were not alleviated since no new data were made available. Notwithstanding this, finally 31 responders were accepted for all the calculations. ORR was also examined by 3 additional subgroups: R-ISS Stage I, II, and III respectively; US vs non-US patients; FLC vs non-FLC MM patients. The ORR was consistent for

age groups below 65 and 65-74, which is reassuring; only few patients (18) were ≥75 years with an ORR of 27.8%, but there seems to be a difference in terms of ORR between US and non-US patients. The difference may be multifactorial, no clear explanation was evident, sample size was small with statistical limitations, the subgroup analysis was not predefined and a difference was also noted according to clinical experience, thus the ORR was higher at sites enrolling 6 patients, i.e. considered more experienced.

Time to response was a median of 4.1 weeks (range 1 to 14), and the median time of exposure was 8 weeks. Even when it is of little value for interpretation as it is a single arm study, OS has been reported by the MAH as a median of 8 months 95% IC (6.3, 11.3). Non-responding patients (PD or NE) showed an OS of 1.9 months for part-2 and 3.8 months for part-1.

The updated median PFS (IRC based) was the same as the first analysis: 3.7 months (95% CI: 2.8, 4.7).

Median OS in US patients was 8.6 months and was not reached in non-US patients. This in contrast to the ORR, which was 31% in US patients and 13.2% in non-US patients. The Applicant has updated the OS data at data cut-off 7 September 2019. The median time of follow-up was 15.0 for US patients versus 14.6 months for non-US patients. Median OS was 8.0 months (95% CI: 6.2, 11.3) in US patients and 8.4 months (95% CI: 3.9, NE) in non-US patients. The difference in ORR and OS results in US and non-US patients at the first analysis is still not understood, however it is reassuring that the OS data with extended follow-up are similar in both US and non-US patients. Sample size is small and confirmatory results from a phase 3 study are awaited.

The absence of a control arm and the small number of patients treated with selinexor impact the interpretation of the clinical benefit. It is not possible to fully elucidate the actual role of the mono-components in this combination. In the light of the data assessed, it seems unlikely that the efficacy in terms of ORR observed in the combination of selinexor 80 mg plus dexamethasone 20 mg (Sd) twice weekly, can be driven by the activity of one of the mono-components and it is unrealistic to believe dexamethasone alone can play the main role in the antitumour activity.

Notwithstanding the above, the ORR observed in the part 2 of this study is 26.2% (32/122) (somehow comparable to the 30% ORR observed in the pomalidomide study), but bearing in mind that the population included here is highly refractory and has received several other therapeutic treatments in previous lines, this implies a more fragile population and a more refractory disease in the STORM study. In fact the population included in the STORM study is more aligned with that included in the belantamab mafodotin pivotal registrational trial (i.e. DREAMM-2) in which an ORR of 32% (97.5% CI: 22%, 44%; N=97) with mDoR of 11 months (95% CI: 4.2, NR) were reported.

The limitation of the unavailability of a control arm in this context calls into question the interpretation of the outcomes, there is no comparable benefit in terms of DoR: median DoR in the STORM study (mITT population part 2) was 4.4 months (95% CI: 3.7, NE). Comparing these results with historic studies such as pomalidomide (San Miguel et al. Lancet Oncol. 2013), control arm with HD dexamethasone showed a median DoR of 6.1 months (ranging from 1.4 to 8.5 months) in patients with at least PR whereas pomalidomide arm showed a DoR of 7 months (ranging from 6 to 9 months). In a daratumumab study (Lonial, Lancet 2016) DoR was reported as 7.4 months (95% IC 5.5 - NE). Further, as described above a mDoR of 11 months (95% CI: 4.2, NR) has been reported for the recently authorised antibody drug conjugate belantamab mafodotin (Lonial et al. Lancet Oncol. 2020). In summary, the overall response rate (as reported by the applicant) in the STORM study is lower with shorter duration of response compared to what is reported in the pomalidomide, daratumumab and belantamab mafodotin studies in RRMM. Furthermore, taking into account the uncertainties related to

the actual number of responders (see above), the duration of the response is for the time being undetermined, which would add even more uncertainty to the overall benefit of this combination.

Of note, data from the BOSTON study comparing the efficacy and safety of selinexor in combination with bortezomib and low-dose dexamethasone (SVd) versus Vd in patients with RRMM, who had received 1 to 3 prior anti-MM regimens became available while this procedure was ongoing. A summary of top line results from this study was provided by the applicant as supportive data. The value of data from the BOSTON study to address remaining uncertainties is recognised, particularly in terms of being able to provide comparative safety data even if neither the disease treatment setting is the same nor the dose used. Further, interpretable randomised data on time to an event endpoint will be available. However, this does not mean that results from the BOSTON study could be used for an initial decision on the benefit/risk ratio of a different combination in a different treatment setting. Selinexor as monotherapy does not appear to be active, and it is only when it is given in combination with other drugs when it can be considered effective. In fact the applicant claims a synergistic effect for some combinations. With this in mind different combinations might provide differential efficacy and therefore discussions/conclusions should be separate ones. In addition, the disease context can also module the response to treatment so that benefit/risk assessment needs to be conducted on the basis of data generated for the specific combination in the intended treatment setting (i.e. the STORM study).

Taking into account the above uncertainties, a more restricted indication on the basis of data reported in the 83 patients of the STORM study whose disease was refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab (penta- refractory) was agreed by the CHMP.

The ORR in the updated population was 25.3% (95% CI: 16.3, 36) and median time to first response 3.9 weeks. Among the 21 responders, 1 had a complete response (CR), 4 had a very good partial response (VGPR), and 16 had a partial response (PR). In addition, 10 patients had a minimal response (MR), 32 had stable disease (SD), and 20 had progressive disease (PD) or were not evaluable. ORR decreases with each subsequent therapy in relapsed/refractory patients and complete responses are rarely achieved. With this in mind, and even if some responses were challenged during previous assessment rounds within the procedure, the reported ORR can be considered as relevant in the intended treatment indication (penta-refractory) and expected to translate into clinically meaningful benefit. The duration of the responses normally decreases after each line of therapy, as the disease becomes increasingly refractory. In the penta-refractory MM population (n=83) of the STORM study the reported median DOR was 3.8 months (95% CI: 2.3, 10.8). Median OS was 8.4 months (95% CI: 5.9; 11.2) with a longer OS for patients having a response of PR or better, however OS data are to be carefully interpreted in the context of a single arm trial.

Additional expert consultation

A Scientific Advisory Group in Oncology (SAG-O) was asked to provide their view on the two following questions:

1. Do available data indicate clinically meaningful efficacy in the sought indication?
2. Is the observed safety profile of selinexor acceptable in the proposed target population?

The SAG-O meeting took place on 30th November 2020. The final minutes on the question 1 are included below. For the minutes on question 2, please see section 2.6.1. Discussion on Clinical Safety.

Do available data indicate clinically meaningful efficacy in the sought indication?

The SAG considered the arguments presented by the Rapporteurs and the applicant company and discussed the claimed indication and the design and results of the "STORM" study.

In terms of the proposed indication, patients with multiple myeloma that recurred or was refractory to multiple therapies including the most active agents, the SAG agreed that there is a large unmet medical need based on the very short survival (median OS was 8.4 months in the STORM trial). In this indication, in the absence of curative treatments, active agents to keep the disease under control for as long as possible are needed. Such agents should also not hamper subsequent treatments as they become available.

The level of activity for selinexor in combination with low-dose dexamethasone in terms of PR and CR in the pivotal STORM trial was claimed to be 26.2% (95% CI: 18.7%; 35.0%). Despite some possible reclassifications based on different adjudication criteria, the antitumour activity has been clearly shown. Furthermore, there was also activity classified as minor response (13.1%).

Antitumour activity attributable to selinexor has been observed despite the fact that trial design was in combination with low-dose dexamethasone, based on indirect comparisons: Although robust estimates of ORR for low dose dexamethasone in this population are not available, high-dose dexamethasone in an earlier line of treatment (likely more effective than low-dose dexamethasone in a more advanced setting of the STORM trial) was associated with 10% ORR (San Miguel et al., 2013).

One SAG member disagreed, pointing out an ORR of >20% was reported as described in a review by Burwick and Sharma 2018. Also, in pretreated patients comparing thalidomide with dexamethasone, the response rate for dexamethasone high was 25% (Kropff, et al. 2012). In a randomised trial in previously pretreated patients comparing carfilzomib vs. lo-dose dexamethasone, the ORR was 11%, MR was 9% and stable disease was 47% for low-dose dexamethasone. There was no PFS and OS benefit for the experimental arm with carfilzomib (Hájek et al. 2017).

Objective response is considered of clinical relevance for patients in this indication provided it is sufficiently likely and of sufficient duration. The ORR associated with selinexor+dexamethasone was claimed to be about 26.2%, and the median duration of response was 4.4 months. In absolute terms, the ORR (also considering re-classification) was rather low and duration of response was considered rather short but still of sufficient magnitude to be of clinical relevance for patients who observe a response and in the range of what observed with alternative treatments in this multiple-relapsed/refractory setting with short expected survival.

Some SAG members disagreed, considering that we do not know, whether the ORR is of relevant clinical benefit in lack of randomised trials and in respect to the limited patient number included.

The magnitude of activity in terms of ORR is in the range of another product that has been recently approved under conditional marketing authorisation (belantamab; 32%; 95% CI:21%; 46%) in a similar population (7 median no. of prior treatments).

Despite all the known biases of responder-analyses, some support was also provided by looking at the association between response and OS with censoring for subsequent treatments, the fact that some responders experienced survival duration of over 24 months, as well as high-level results from the BOSTON trial reporting a beneficial effect of selinexor in combination with bortezomib and dexamethasone in terms of PFS in earlier stages of treatment of the disease (1-3 prior lines). Selinexor did not appear to hamper the number of subsequent treatments. One SAG member added that it is interesting to know how many patients with myeloma will come to the moment they are fit enough to be included for this treatment. The population in the Boston and Storm trials is heavily selected.

One SAG member also pointed out that there might, be also a bias in selecting patients. "Refractory" has not been clearly defined (primary or secondary refractory?). Additionally, it is not clear whether

patients have been in last line, as a remarkable proportion of patients received a subsequent therapy. It is not clear, whether is due to the response by selixenor or whether the patient had further treatment options besides selixenor.

The probability of observing a response and disease control for some months, and any existing uncertainties about other outcomes, should be part of individual clinical benefit-risk decisions taking also expected toxicity into account. It is understood that, as for many treatment options in this difficult stage of treatment of the disease, treatment with selinexor + dexamethasone may not be the preferred treatment option for all patients in the claimed indication. (One SAG member questioned how the claimed patient population was defined.)

In conclusion, the SAG agreed that in the claimed indication, given the high unmet need, the observed ORR is expected to be associated with a clinical benefit in patients who respond and although low, the activity is considered sufficient to be of benefit to some patients in the proposed indication. However, two SAG members considered that we know that ORR is not the relevant endpoint to consider a benefit for the overall population. There is no comparison of PFS and OS in this patient population to other options. Also, one member considered that the first endpoint should have been quality of life.

The SAG found that the applicant company has conducted a valuable exploration of possible biomarkers for efficacy. This effort should be pursued in order to optimise treatment decisions by identifying patients most likely to respond.

The SAG regretted the lack of a comparative study to confirm an effect on OS, PFS, and health-related quality of life in the claimed indication. Some members underlined feasibility of a randomised controlled trial in terms of number of patients while others underlined the difficulty of conducting randomised trials in this advanced setting. The BOSTON study may provide some level of support to confirm the safety and efficacy of the drug in the claimed indication although extrapolations across different stages of treatment of the disease require strong assumptions.

Additional efficacy data needed in the context of a conditional MA

Based on the observed efficacy in study KCP-330-012/STORM, a clinical benefit for selinexor in combination with dexamethasone can be considered established, but a confirmation from a phase 3 comparative study is needed in order to confirm the magnitude of the effect.

To provide additional evidence of the clinical benefits observed in study KCP-330-012/STORM and in order to fulfil a CMA, the applicant is requested by the CHMP to provide the final results of the BOSTON study, a phase 3, randomised, active comparator-controlled, open-label, multicentre (sites worldwide) study to compare the efficacy and assess the safety of selinexor plus bortezomib plus low-dose dexamethasone (SVd) versus bortezomib plus low dose dexamethasone (Vd) in ~364 adult patients with RRMM who have received 1 to 3 prior anti-MM regimens, with data cut-off February 2021) as a Specific Obligation.

2.5.4. Conclusions on the clinical efficacy

The reported ORR of 25.3% (95% CI: 16.3, 36) in the penta-refractory group of patients (n=83) from the STORM study can be considered as relevant in the intended treatment setting and expected to translate into clinically meaningful benefit in the proposed target population.

However, efficacy results from a comparative study is needed in order to confirm the magnitude of the effect.

The CHMP considers the following measure necessary to address the missing efficacy data in the context of a conditional MA:

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 results of the phase 3, KCP-330-023/BOSTON study (data cut off February 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.

2.6. Clinical safety

Patient exposure

The safety evaluation is based on data from 1265 patients from 8 clinical trials evaluating selinexor in advanced, heavily pretreated, haematological malignancies including 552 patients with MM.

Of these, 214 patients from studies KPT-330-012 and KPT-330-001 represent the main safety dataset. Study KPT-330-012 (STORM) is the pivotal study; it is a phase 2, single arm, open-label study of Sd in patients with heavily pre-treated RRMM. The study initially enrolled 79 patients in Part 1 followed by Part 2, which was a separate cohort, with 123 patients. Part 2 included patients with penta-exposed and triple-class refractory MM that was refractory to the last line of therapy. Study KPT-330-001 was a Phase 1, open-label, dose-escalation study. In this study, 12 of the 285 patients included had heavily pre-treated RRMM and were treated with Sd.

The applicant has provided an analysis of data from patients included in the safety analyses based on various pools:

- All Heme – Single Agent (±dex) Pool: Comprised of 996 patients with different types of haematologic malignancies (All HM) from Studies 001, KCP-330-008, KCP-330-009, KCP-330010, STORM, and KCP-330-013. Patients received single agent selinexor (with or without dexamethasone).
- All MM Pool: Comprised of 552 patients with MM who were treated in Studies 001, STORM, and the ongoing studies KCP-330-017 and KCP-330-023 with different selinexor dose levels and combination treatment regimens.

The safety data from the All Heme – Single Agent (±dex) Pool and the All MM Pool were combined for some analyses (total safety population).

In the All MM Pool Sd group, 214 patients received at least 1 dose of selinexor. The median duration of exposure for the Sd group was 8.5 weeks (range 1 to 76) with a median of 11 doses (range 1 to 135) received and a median total dose of 830 mg (range 80 to 6220). Most patients in the Sd group received treatment for either 4 to <12 weeks (85 [39.7%] patients) or 12 to <24 weeks (51 [23.8%] patients). The median dose intensity was 112.4 mg/week (range 22 to 240) with a relative dose intensity of 77.8% (range 29 to 116) relative to starting dose. The median percent dose compliance was 100% (range 64 to 100).

Table 40 Disposition Overall and by Selected Treatment Regimens within the All MM Pool

Disposition Category	All MM (N = 552) n (%)	S(80 mg)+d (N = 214) n (%)	Other S±d (N = 71) n (%)
Enrolled Patients Who Received At Least One Dose of Selinexor (Safety Population)	552 (100.0)	214 (100.0)	71 (100.0)
Patients Who Terminated Treatment of Selinexora	414 (75.0)	214 (100.0)	71 (100.0)
Disease Progression/Death due to Disease Progression	209 (50.5)	120 (56.1)	36 (50.7)
Death due to Reasons Other Than Disease Progression	11 (2.7)	0	6 (8.5)
Adverse Event (Related to Selinexor)/Toxicity of Study Drug	61 (14.7)	38 (17.8)	3 (4.2)
Adverse Event (Not Related to Selinexor)	32 (7.7)	22 (10.3)	1 (1.4)
Other Reasons	95 (22.9)	34 (15.9)	25 (35.2)
Missing	6 (1.4)	0	0
Patients Contacted for Survival Follow-up	203 (36.8)	122 (57.0)	15 (21.1)

Source: Table 14.1.2.3.1.1
(Database Cutoff Date: 2019-09-07)
[a] The denominator for the reasons for termination is the number of patients who terminated treatment of selinexor.
Note: The All MM Pool includes all multiple myeloma patients dosed with selinexor (001, 012, 017, 023).

Table 41 Disposition by Study in the Total Safety Population

Disposition Category	001 (N = 285) n (%)	008 (N = 213) n (%)	009 (N = 254) n (%)	010 (N = 26) n (%)	012 (N = 202) n (%)	013 (N = 16) n (%)	017 (N = 132) n (%)	023 (N = 137) n (%)	Total (N = 1265) n (%)
Enrolled Patients Who Received At Least One Dose of Selinexor (Safety Population)	285 (100.0)	213 (100.0)	254 (100.0)	26 (100.0)	202 (100.0)	16 (100.0)	132 (100.0)	137 (100.0)	1265 (100.0)
Patients Who Terminated Treatment of Selinexor[a]	285 (100.0)	213 (100.0)	214 (84.3)	26 (100.0)	202 (100.0)	16 (100.0)	104 (78.8)	27 (19.7)	1087 (85.9)
Disease Progression/Death due to Disease Progression	163 (57.2)	85 (39.9)	124 (57.9)	13 (50.0)	115 (56.9)	6 (37.5)	46 (44.2)	8 (29.6)	560 (51.5)
Death due to Reasons Other Than Disease Progression	18 (6.3)	10 (4.7)	0	0	0	0	0	6 (22.2)	34 (3.1)
Adverse Event (Related to Selinexor)/Toxicity of Study Drug	11 (3.9)	26 (12.2)	30 (14.0)	4 (15.4)	37 (18.3)	3 (18.8)	17 (16.3)	3 (11.1)	131 (12.1)
Adverse Event (Not Related to Selinexor)	10 (3.5)	28 (13.1)	11 (5.1)	4 (15.4)	20 (9.9)	2 (12.5)	6 (5.8)	3 (11.1)	84 (7.7)
Other Reasons	83 (29.1)	64 (30.0)	27 (12.6)	5 (19.2)	30 (14.9)	5 (31.3)	29 (27.9)	7 (25.9)	250 (23.0)
Missing	0	0	22 (10.3)	0	0	0	6 (5.8)	0	28 (2.6)
Patients Contacted for Survival Follow-up	43 (15.1)	70 (32.9)	98 (38.6)	4 (15.4)	120 (59.4)	0	66 (50.0)	0	401 (31.7)

Source: Table 14.1.3.2.1.1
(Database Cutoff Date: 2019-09-07)
[a] The denominator for the reasons for termination is the number of patients who terminated treatment of selinexor.

Table 42 Patient exposure to study treatment of selinexor plus dexamethasone – Study STORM (Safety Analysis Population)

	Part 2 N=123		Part 1 N=79	
Category	**Selinexor**	**Dex**	**Selinexor**	**Dex**
Duration of Study Treatment Exposure (Weeks) [1]				
n	123	--	79	--
Median	9.0	--	8.0	--
Mean (SD)	12.3 (11.72)	--	11.6 (10.97)	--
Min, Max	1, 76	--	1, 58	--
Duration Study Treatment Exposure (Weeks), n (%)				
≥ 2	116 (94.3)	--	75 (94.9)	--
≥ 4	103 (83.7)	--	63 (79.7)	--
≥ 8	71 (57.7)	--	40 (50.6)	--
≥ 12	46 (37.4)	--	29 (36.7)	--
≥ 16	36 (29.3)	--	21 (26.6)	--
≥ 24	17 (13.8)		11 (13.9)	
≥ 32	6 (4.9)	--	6 (7.6)	--
≥ 36	3 (2.4)	--	4 (5.1)	--
Missing	0	--	0	--
Total Dose (mg) Received				
Median	920.0	256.0	720.0	240.0
Mean (SD)	1229.1 (1038.77)	370.5 (362.18)	1184.3 (1164.09)	377.8 (381.04)
Min, Max	160, 6220	40, 2220	80, 5600	4, 2320
Total Dose (mg) Received n (%)				
0-500 (Sel) /0-160 (dex)	28 (22.8)	39 (31.7)	30 (38.0)	31 (39.2)
501-1000 /161- 480	40 (32.5)	56 (45.5)	18 (22.8)	25 (31.6)
1001-1500 /481-960	25 (20.3)	21 (17.1)	15 (19.0)	18 (22.8)
1501-2000 / > 960	11 (8.9)	7 (5.7)	4 (5.1)	5 (6.3)
> 2000/NA	19 (15.4)	--	12 (15.2)	--
Average Dose Received per Week (mg/Week) [2]				
Median	113.6	33.3	113.8	36.9
Mean (SD)	117.2 (35.83)	32.1 (8.83)	117.4 (32.97)	33.5 (8.55)

Min, Max	22, 240	7, 60	53, 200	4, 50
Percent Compliance for Study Treatment [3]				
Median	100.0		100.0	
Mean (SD)	98.4 (5.26)		98.2 (5.49)	
Min, Max	67, 100		67, 100	
Patients with a Dose Reduction, n (%)				
Yes	76 (61.8)	26 (21.1)	37 (46.8)	14 (17.7)
Patients with a Dose Interruption/Withheld, n (%)				
	121 (98.4)	119 (96.7)	76 (96.2)	71 (89.9)
Patients Who Received Sd Following Dose Interruption/Withheld, n (%)				
	86 (69.9)		46 (58.2)	

Source: Table 14.1.3.2; Table 14.1.3.7.
NA=not applicable; SD=standard deviation.
[1] Average dose received = total dose (mg) received/number of doses received.
[2] Defined as 100*[(number of prescribed doses - number of missed doses)/number of prescribed doses
[3] ≥70% of prescribed doses

Adverse events

Table 43 Summary of Adverse Events for the All Heme – Single Agent (±dex) Pool, All MM Pool, the All MM Pool Sd Group, and Total Safety Population (Safety Population)

Patients with at least 1:	All Heme (N=996) n (%)	All MM Pool (N=552) n (%)	All MM Pool S(80 mg)+d (N=214) n (%)	Total Safety Population (N=1265) n (%)
TEAE	991 (99.5)	537 (97.3)	214 (100)	1245 (98.4)
Treatment-Related TEAE	945 (94.9)	513 (92.9)	211 (98.6)	1179 (93.2)
TEAE leading to dose modification[a]	468 (47.0)	321 (58.2)	158 (73.8)	631 (49.9)
Dose reduction	239 (24.0)	204 (37.0)	107 (50.0)	336 (26.6)
Dose interruption	390 (39.2)	261 (47.3)	126 (58.9)	525 (41.5)
Severity Grade 3/4[b]	867 (87.0)	453 (82.1)	202 (94.4)	1049 (82.9)
TEAE leading to DC	276 (27.7)	102 (18.5)	60 (28.0)	309 (24.4)
Treatment-Related TEAE leading to DC	163 (16.4)	69 (12.5)	38 (17.8)	187 (14.8)
SAE	626 (62.9)	271 (49.1)	130 (60.7)	722 (57.1)
Treatment-Related SAE	295 (29.6)	128 (23.2)	59 (27.6)	346 (27.4)
TEAE leading to death	157 (15.8)	43 (7.8)	20 (9.3)	173 (13.7)
Treatment-Related TEAE leading to death	31 (3.1)	10 (1.8)	4 (1.9)	35 (2.8)

Note: The All Heme – Single Agent (±dex) Pool includes all single agent selinexor (with or without dexamethasone) hematological studies (001, 008, 009, 010, 012, 013).
Note: The All MM Pool includes all multiple myeloma patients dosed with selinexor (001, 012, 017, 023).
[a] The number of patients with dose modification is not necessarily equal to the sum of the number of patients who had a modified dose or had drug interruption since the same patient could fall into more than one of these categories.
[b] Severity was designated as the maximum severity for the event.

Table 44 Overall Summary of TEAEs – Study KCP-330-012 (Safety Analysis Population)

Patients with at least 1 event by category	Part 2 (N = 123) n (%)	Part 1 (N = 79) n (%)	Total (N = 202) n (%)
All Causality [1]			
TEAE	123 (100)	79 (100)	202 (100)
Grade 3 or 4 TEAE	115 (93.5)	75 (94.9)	190 (94.1)
TESAE	78 (63.4)	45 (57.0)	123 (60.9)
TEAE Leading to Dose Modification	97 (78.9)	61 (77.2)	158 (78.2)
TEAE Leading to Dose Hold	80 (65.0)	46 (58.2)	126 (62.4)
TEAE Leading to Dose Reduction	72 (58.5)	35 (44.3)	107 (53.0)
TEAE Leading to Treatment Discontinuation	39 (31.7)	20 (25.3)	59 (29.2)
TEAE with an Outcome of Death	12 (9.8)	8 (10.1)	20 (9.9)
Treatment Related [2]			
TEAE	121 (98.4)	78 (98.7)	199 (98.5)
Grade 3 or 4 TEAE	110 (89.4)	69 (87.3)	179 (88.6)
TESAE	38 (30.9)	21 (26.6)	59 (29.2)
TEAE Leading to Dose Modification	88 (71.5)	54 (68.4)	142 (70.3)
TEAE Leading to Dose Hold	64 (52.0)	37 (46.8)	101 (50.0)
TEAE Leading to Dose Reduction	70 (56.9)	32 (40.5)	102 (50.5)
TEAE Leading to Treatment Discontinuation	24 (19.5)	13 (16.5)	37 (18.3)
TEAE with an Outcome of Death	3 (2.4)	1 (1.3)	4 (2.0)

Source: Table 14.3.1.1.
Abbreviations: TEAE=treatment-emergent adverse event; TESAE = serious TEAE
1. 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.
2. TEAEs with a relationship of Possible, Probable, or Definite to either selinexor or dexamethasone per Investigator are considered related to study treatment.
Note: Percentages are based on the number of all-treated patients in each treatment group. A TEAE is defined as an AE that emerged or worsened from first dose to 30 days after last dose.

Common adverse events

All MM Pool - Sd group

In the Sd group, all 214 (100%) patients had at least 1 TEAE. The most common nonhaematological TEAEs in the Sd group (occurring in ≥25% of patients) were nausea (160 [74.8%] patients), fatigue (142 [66.4%] patients), decreased appetite (120 [56.1%] patients), decreased weight (105 [49.1%] patients), diarrhoea (101[47.2%] patients), vomiting (91 [42.5%] patients), hyponatraemia (85 [39.7%] patients), and dyspnoea (56 [26.2%] patients). The most common haematological TEAEs in the All MM Pool Sd group (occurring in ≥25% of patients) were thrombocytopenia (161 [75.2%] patients), anaemia (129[60.3%] patients), neutropenia (78 [36.4%] patients), and leukopenia (64 [29.9%] patients.

Table 45 Treatment-Emergent Adverse Events Occurring in ≥10% of Patients in the All MM Pool Overall and by Selected Treatment Regimens within the All MM Pool

MedDRA System Organ Class MedDRA Preferred Term	All MM (N = 552) n (%)	S(80 mg)+d (N = 214) n (%)	KCP-330-012/STORM Part 2 (N = 123) n (%)	Other S±d (N = 71) n (%)
Blood and lymphatic system disorders				
Thrombocytopenia	346 (62.7)	161 (75.2)	92 (74.8)	43 (60.6)
Anaemia	264 (47.8)	129 (60.3)	82 (66.7)	34 (47.9)
Neutropenia	185 (33.5)	78 (36.4)	49 (39.8)	25 (35.2)
Leukopenia	108 (19.6)	64 (29.9)	41 (33.3)	8 (11.3)
Eye disorders				
Vision blurred	75 (13.6)	30 (14.0)	13 (10.6)	14 (19.7)
Gastrointestinal disorders				
Nausea	348 (63.0)	160 (74.8)	88 (71.5)	55 (77.5)
Diarrhoea	215 (38.9)	101 (47.2)	58 (47.2)	26 (36.6)
Vomiting	192 (42.5)	91 (42.5)	48 (39.0)	35 (49.3)
Constipation	117 (21.2)	50 (23.4)	27 (22.0)	13 (18.3)
Abdominal pain	58 (10.5)	23 (10.7)	12 (9.8)	8 (11.3)
General disorders and administration site conditions				
Fatigue	317 (57.4)	142 (66.4)	77 (62.6)	52 (73.2)
Pyrexia	87 (15.8)	36 (16.8)	20 (16.3)	22 (31.0)
Asthenia	72 (13.0)	29 (13.6)	22 (17.9)	14 (19.7)
Oedema peripheral	59 (10.7)	20 (9.3)	14 (11.4)	7 (9.9)
Infections and infestations				
Pneumonia	62 (11.2)	27 (12.6)	21 (17.1)	12 (16.9)
Investigations				
Weight decreased	181 (32.8)	105 (49.1)	62 (50.4)	28 (39.4)
Metabolism and nutrition disorders				
Decreased appetite	269 (48.7)	120 (56.1)	70 (56.9)	47 (66.2)
Hyponatraemia	154 (27.9)	85 (39.7)	46 (37.4)	32 (45.1)
Dehydration	79 (14.3)	31 (14.5)	13 (10.6)	27 (38.0)
Hypokalaemia	74 (13.4)	32 (15.0)	24 (19.5)	9 (12.7)
Hyperglycaemia	56 (10.1)	33 (15.4)	15 (12.2)	6 (8.5)
Musculoskeletal and connective tissue disorders				
Back pain	74 (13.4)	22 (10.3)	11 (8.9)	18 (25.4)
Nervous system disorders				
Dizziness	87 (15.8)	32 (15.0)	19 (15.4)	12 (16.9)

MedDRA System Organ Class MedDRA Preferred Term	All MM (N = 552) n (%)	S(80 mg)+d (N = 214) n (%)	KCP-330-012/STORM Part 2 (N = 123) n (%)	Other S±d (N = 71) n (%)
Dysgeusia	70 (12.7)	24 (11.2)	10 (8.1)	12 (16.9)
Headache	61 (11.1)	25 (11.7)	11 (8.9)	8 (11.3)
Psychiatric disorders				
Insomnia	75 (13.6)	36 (16.8)	22 (17.9)	5 (7.0)
Confusional state	68 (12.3)	31 (14.5)	15 (12.2)	12 (16.9)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	119 (21.6)	56 (26.2)	28 (22.8)	18 (25.4)
Cough	83 (15.0)	34 (15.9)	18 (14.6)	14 (19.7)
Epistaxis	59 (10.7)	29 (13.6)	15 (12.2)	13 (18.3)

Source: Table 14.3.3.2.2.1.1.1.3, CSR KPT-330-012 Table 14.3.2.1.1
(Database Cutoff Date: 2019-09-07)
Note: This table uses MedDRA version 22.0 for Study 012, and MedDRA version 20.1 for all other studies.
Note: Selected System Organ Classes are recoded to aggregate medically similar SOCs.
Note: Selected Preferred Terms are recoded to aggregate medically similar PTs.
Note: The All MM Pool includes all multiple myeloma patients dosed with selinexor (001, 012, 017, 023).
Note: The ≥10% threshold is based off of the All MM column.

In Sd group, 205 (95.8%) patients had at least 1 ≥Grade 3 TEAE, 99 (46.3%) patients had at least 1 Grade 4 TEAE, and 20 (9.3%) patients had at least 1 Grade 5 TEAE.

The most frequently reported Grade ≥3 AEs in the Sd group (occurring in ≥10% of patients) were thrombocytopenia (139 [65%] patients), anaemia (94 [43.9%] patients), hyponatraemia (50 [23.4%] patients), neutropenia (49 [22.9%] patients), fatigue (43 [20.1%] patients), leukopenia (31 [14.5%] patients), lymphopenia (23 [10.7%] patients). Of these, Grade 4 TEAEs included thrombocytopenia (87 [40.7%] patients), neutropenia (11 [5.1%] patients), lymphopenia. (7 [3.3%] patients), anaemia (5 [2.3%] patients), hyponatraemia (2 [0.9%] patients) and leukopenia (1 [0.5%] patients). The majority of Grade 3 or 4 TEAEs of thrombocytopenia were not typically associated with bleeding.

Of the 139 (65.0%) patients with ≥Grade 3 TEAE of thrombocytopenia, concurrent bleeding events (concurrency defined as ±5 days) of ≥Grade 3 were reported in 7 (5.0%; 7/139) patients. The event terms for bleeding events by PT included: rectal haemorrhage (2 patients), subdural haematoma (2 patients), and epistaxis, tumour haemorrhage, and procedural haemorrhage (1 patient each).

Table 46
Severe (≥ Grade 3) TEAEs Occurring in ≥ 2% of Patients Treated with Sd, by SOC and PT - All Causalities – Study KCP-330-012 (Safety Analysis Population)

System Organ Class Preferred Term	Part 2 (N = 123) n (%)	Part 1 (N = 79) n (%)	Total (N = 202) n (%)
Patient with ≥ 1 TEAE	117 (95.1)	76 (96.2)	193 (95.5)
Blood and lymphatic system disorders	**92 (74.8)**	**63 (79.7)**	**155 (76.7)**
Thrombocytopenia	76 (61.8)	55 (69.6)	131 (64.9)
Anaemia	55 (44.7)	31 (39.2)	86 (42.6)
Neutropenia	27 (22.0)	20 (25.3)	47 (23.3)
Leukopenia	17 (13.8)	11 (13.9)	28 (13.9)
Lymphopenia	14 (11.4)	7 (8.9)	21 (10.4)
Febrile neutropenia	2 (1.6)	3 (3.8)	5 (2.5)
Gastrointestinal disorders	25 (20.3)	14 (17.7)	39 (19.3)
Nausea	12 (9.8)	6 (7.6)	18 (8.9)
Diarrhoea	9 (7.3)	4 (5.1)	13 (6.4)

Vomiting	5 (4.1)	3 (3.8)	8 (4.0)
General disorders and administration site conditions	**41 (33.3)**	**16 (20.3)**	**57 (28.2)**
Fatigue	26 (21.1)	14 (17.7)	40 (19.8)
Asthenia	8 (6.5)	1 (1.3)	9 (4.5)
General physical health deterioration	7 (5.7)	0	7 (3.5)
Infections and infestations	**35 (28.5)**	**16 (20.3)**	**51 (25.2)**
Pneumonia	12 (9.8)	3 (3.8)	15 (7.4)
Sepsis	13 (10.6)	1 (1.3)	14 (6.9)
Urinary tract infection	3 (2.4)	1 (1.3)	4 (2.0)
Influenza	1 (0.8)	4 (5.1)	5 (2.5)
Injury, poisoning and procedural complications	**10 (8.1)**	**7 (8.9)**	**17 (8.4)**
Fall	2 (1.6)	2 (2.5)	4 (2.0)
Metabolism and nutritional disorders	**51 (41.5)**	**35 (44.3)**	**86 (42.6)**
Hyponatraemia	27 (22.0)	19 (24.1)	46 (22.8)
Hyperglycaemia	8 (6.5)	9 (11.4)	17 (8.4)
Decreased appetite	8 (6.5)	4 (5.1)	12 (5.9)
Dehydration	4 (3.3)	3 (3.8)	7 (3.5)
Hypokalemia	8 (6.5)	1 (1.3)	9 (4.5)
Hypercreatininaemia	0	1 (1.3)	1 (0.5)
Hypophosphataemia	4 (3.3)	3 (3.8)	7 (3.5)
Hypercalcaemia	0	4 (5.1)	4 (2.0)
Hyperkalaemia	4 (3.3)	0	4 (2.0)
Nervous system disorders	**11 (8.9)**	**4 (5.1)**	**15 (7.4)**
Syncope	5 (4.1)	3 (3.8)	8 (4.0)
Psychiatric disorders	**12 (9.8)**	**8 (10.1)**	**20 (9.9)**
Confusional state	5 (4.1)	6 (7.6)	11 (5.4)
Mental status changes	3 (2.4)	1 (1.3)	4 (2.0)

System Organ Class Preferred Term	Part 2 (N = 123) n (%)	Part 1 (N = 79) n (%)	Total (N = 202) n (%)
Insomnia	2 (1.6)	2 (2.5)	4 (2.0)
Renal and urinary disorders	**6 (4.9)**	**4 (5.1)**	**10 (5.0)**
Acute kidney injury	2 (1.6)	4 (5.1)	6 (3.0)
Respiratory, thoracic, and mediastinal disorders	**15 (12.2)**	**7 (8.9)**	**22 (10.9)**
Dyspnoea	5 (4.1)	4 (5.1)	9 (4.5)

Source Table 14.3.2.1.5.
Note: Adverse Events are coded using MedDRA version 22.0. Patients are counted once within each system organ class and preferred term. Percentages are based on the number of all-treated patients in each treatment group. A treatment- emergent AE (TEAE) is defined as an AE that emerged or worsened in the period from date of first dose to 30 days after the date of last dose. The date of onset of the AE was used to determine treatment emergence.

Table 47 Treatment-Emergent Adverse Events by Study Occurring in ⩾10% of Patients in the Total Safety Population

MedDRA System Organ Class MedDRA Preferred Term	001 (N = 285) n (%)	008 (N = 213) n (%)	009 (N = 254) n (%)	010 (N = 26) n (%)	012 (N = 202) n (%)	013 (N = 16) n (%)	017 (N = 132) n (%)	023 (N = 137) n (%)	Total (N = 1265) n (%)
Blood and lymphatic system disorders									
Thrombocytopenia	170 (59.6)	76 (35.7)	139 (54.7)	15 (57.7)	152 (75.2)	3 (18.8)	79 (59.8)	63 (46.0)	697 (55.1)
Anaemia	152 (53.3)	60 (28.2)	83 (32.7)	7 (26.9)	121 (59.9)	3 (18.8)	62 (47.0)	39 (28.5)	527 (41.7)
Neutropenia	99 (34.7)	29 (13.6)	70 (27.6)	6 (23.1)	72 (35.6)	2 (12.5)	69 (52.3)	13 (9.5)	360 (28.5)
Leukopenia	50 (17.5)	15 (7.0)	15 (5.9)	5 (19.2)	61 (30.2)	0	28 (21.2)	8 (5.8)	182 (14.4)
Eye disorders									
Vision blurred	67 (23.5)	18 (8.5)	24 (9.4)	1 (3.8)	23 (11.4)	3 (18.8)	24 (18.2)	7 (5.1)	167 (13.2)
Gastrointestinal disorders									
Nausea	194 (68.1)	125 (58.7)	148 (58.3)	14 (53.8)	150 (74.3)	10 (62.5)	82 (62.1)	52 (38.0)	775 (61.3)
Diarrhoea	121 (42.5)	77 (36.2)	75 (29.5)	9 (34.6)	95 (47.0)	4 (25.0)	57 (43.2)	31 (22.6)	469 (37.1)
Vomiting	125 (43.9)	63 (29.6)	72 (28.3)	9 (34.6)	85 (42.1)	3 (18.8)	44 (33.3)	23 (16.8)	424 (33.5)
Constipation	75 (26.3)	53 (24.9)	74 (29.1)	5 (19.2)	48 (23.8)	5 (31.3)	37 (28.0)	17 (12.4)	314 (24.8)
Abdominal pain	46 (16.1)	22 (10.3)	37 (14.6)	4 (15.4)	19 (9.4)	0	16 (12.1)	11 (8.0)	155 (12.3)
General disorders and administration site conditions									
Fatigue	201 (70.5)	100 (46.9)	116 (45.7)	9 (34.6)	132 (65.3)	10 (62.5)	79 (59.8)	44 (32.1)	691 (54.6)
Pyrexia	74 (26.0)	49 (23.0)	43 (16.9)	10 (38.5)	33 (16.3)	2 (12.5)	18 (13.6)	11 (8.0)	240 (19.0)
Asthenia	29 (10.2)	47 (22.1)	53 (20.9)	8 (30.8)	28 (13.9)	0	13 (9.8)	16 (11.7)	194 (15.3)
Oedema peripheral	46 (16.1)	43 (20.2)	26 (10.2)	6 (23.1)	19 (9.4)	0	21 (15.9)	11 (8.0)	172 (13.6)
Infections and infestations									
Pneumonia	36 (12.6)	33 (15.5)	21 (8.3)	3 (11.5)	26 (12.9)	1 (6.3)	13 (9.8)	12 (8.8)	145 (11.5)
Investigations									
Weight decreased	90 (31.6)	41 (19.2)	78 (30.7)	3 (11.5)	101 (50.0)	0	40 (30.3)	8 (5.8)	361 (28.5)
Metabolism and nutrition disorders									
Decreased appetite	180 (63.2)	117 (54.9)	101 (39.8)	9 (34.6)	113 (55.9)	7 (43.8)	67 (50.8)	35 (25.5)	629 (49.7)
Hyponatraemia	113 (39.6)	59 (27.7)	26 (10.2)	7 (26.9)	81 (40.1)	0	28 (21.2)	9 (6.6)	323 (25.5)
Hypokalaemia	55 (19.3)	20 (9.4)	20 (7.9)	5 (19.2)	29 (14.4)	1 (6.3)	26 (19.7)	7 (5.1)	163 (12.9)
Dehydration	61 (21.4)	19 (8.9)	20 (7.9)	2 (7.7)	29 (14.4)	0	19 (14.4)	2 (1.5)	152 (12.0)
Nervous system disorders									
Dizziness	57 (20.0)	33 (15.5)	30 (11.8)	5 (19.2)	31 (15.3)	1 (6.3)	32 (24.2)	11 (8.0)	200 (15.8)
Dysgeusia	58 (20.4)	22 (10.3)	25 (9.8)	2 (7.7)	20 (9.9)	2 (12.5)	25 (18.9)	9 (6.6)	163 (12.9)
Psychiatric disorders									
Insomnia	31 (10.9)	21 (9.9)	15 (5.9)	1 (3.8)	33 (16.3)	1 (6.3)	17 (12.9)	17 (12.4)	136 (10.8)
Confusional state	51 (17.9)	20 (9.4)	10 (3.9)	1 (3.8)	27 (13.4)	0	16 (12.1)	9 (6.6)	134 (10.6)
Respiratory, thoracic and mediastinal disorders									
Dyspnoea	89 (31.2)	50 (23.5)	35 (13.8)	5 (19.2)	51 (25.2)	1 (6.3)	35 (26.5)	10 (7.3)	276 (21.8)
Cough	57 (20.0)	31 (14.6)	40 (15.7)	5 (19.2)	29 (14.4)	0	23 (17.4)	13 (9.5)	198 (15.7)
Epistaxis	50 (17.5)	42 (19.7)	6 (2.4)	0	26 (12.9)	0	12 (9.1)	5 (3.6)	141(11.1)

Source: Table 14.3.3.2.3.1.1.1.3
(Database Cutoff Date: 2019-09-07)
Note: This table uses MedDRA version 22.0 for Study 012, and MedDRA version 20.1 for all other studies.
Note: Selected System Organ Classes are recoded to aggregate medically similar SOCs.
Note: Selected Preferred Terms are recoded to aggregate medically similar PTs.

Table 48 Treatment-Emergent Adverse Events by Maximum Severity Grade Occurring in ≥10% of Patients in the Total Safety Population (N=1265)

MedDRA System Organ Class MedDRA Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Grade 3/4/5 n (%)	Missing n (%)	Total n (%)
Blood and lymphatic system disorders								
Thrombocytopenia	60 (4.7)	83 (6.6)	218 (17.2)	336 (26.6)	0	554 (43.8)	0	697 (55.1)
Anaemia	36 (2.8)	156 (12.3)	314 (24.8)	21 (1.7)	0	335 (26.5)	0	527 (41.7)
Neutropenia	23 (1.8)	55 (4.3)	160 (12.6)	122 (9.6)	0	282 (22.3)	0	360 (28.5)
Leukopenia	27 (2.1)	46 (3.6)	79 (6.2)	29 (2.3)	0	108 (8.5)	1 (0.1)	182 (14.4)
Eye disorders								
Vision blurred	132 (10.4)	28 (2.2)	6 (0.5)	0	0	6 (0.5)	1 (0.1)	167 (13.2)
Gastrointestinal disorders								
Nausea	365 (28.9)	345 (27.3)	65 (5.1)	0	0	65 (5.1)	0	775 (61.3)
Diarrhoea	281 (22.2)	137 (10.8)	49 (3.9)	1 (0.1)	1 (0.1)	51 (4.0)	0	469 (37.1)
Vomiting	253 (20.0)	129 (10.2)	41 (3.2)	0	0	41 (3.2)	1 (0.1)	424 (33.5)
Constipation	223 (17.6)	80 (6.3)	11 (0.9)	0	0	11 (0.9)	0	314 (24.8)
Abdominal pain	82 (6.5)	53 (4.2)	19 (1.5)	0	1 (0.1)[a]	20 (1.6)	0	155 (12.3)
General disorders and administration site conditions								
Fatigue	192 (15.2)	328 (25.9)	169 (13.4)	0	2 (0.2)	171 (13.5)	0	691 (54.6)
Pyrexia	142 (11.2)	72 (5.7)	22 (1.7)	0	2 (0.2)	24 (1.9)	2 (0.2)	240 (19.0)
Asthenia	58 (4.6)	80 (6.3)	56 (4.4)	0	0	56 (4.4)	0	194 (15.3)
Oedema peripheral	118 (9.3)	42 (3.3)	10 (0.8)	1 (0.1) [a]	0	11 (0.9)	1 (0.1)	172 (13.6)
Infections and infestations								
Pneumonia	2 (0.2)	35 (2.8)	70 (5.5)	8 (0.6)	30 (2.4)	108 (8.5)	0	145 (11.5)
Investigations								
Weight decreased	172 (13.6)	172 (13.6)	17 (1.3)	0	0	17 (1.3)	0	361 (28.5)
Metabolism and nutrition disorders								
Decreased appetite	249 (19.7)	301 (23.8)	77 (6.1)	1 (0.1)	0	78 (6.2)	1 (0.1)	629 (49.7)
Hyponatraemia	148 (11.7)	0	168 (13.3)	5 (0.4)	2 (0.2)	175 (13.8)	0	323 (25.5)
Hypokalaemia	83 (6.6)	37 (2.9)	40 (3.2)	3 (0.2)	0	43 (3.4)	0	163 (12.9)
Dehydration	26 (2.1)	86 (6.8)	38 (3.0)	2 (0.2)	0	40 (3.2)	0	152 (12.0)
Nervous system disorders								
Dizziness	156 (12.3)	38 (3.0)	4 (0.3)	0	1 (0.1)	5 (0.4)	1 (0.1)	200 (15.8)
Dysgeusia	112 (8.9)	51 (4.0)	0	0	0	0	0	163 (12.9)
Psychiatric disorders								
Insomnia	83 (6.6)	45 (3.6)	8 (0.6)	0	0	8 (0.6)	0	136 (10.8)
Confusional state	51 (4.0)	52 (4.1)	30 (2.4)	1 (0.1)	0	31 (2.5)	0	134 (10.6)
Respiratory, thoracic and mediastinal disorders								
Dyspnoea	137 (10.8)	85 (6.7)	42 (3.3)	10 (0.8)	2 (0.2)	54 (4.3)	0	276 (21.8)
Cough	132 (10.4)	64 (5.1)	2 (0.2)	0	0	2 (0.2)	0	198 (15.7)
Epistaxis	107 (8.5)	19 (1.5)	14 (1.1)	1 (0.1)	0	15 (1.2)	0	141 (11.1)

Source: Table 14.3.3.2.3.1.2.1.3
(Database Cutoff Date: 2019-09-07)
Note: This table uses MedDRA version 22.0 for Study 012, and MedDRA version 20.1 for all other studies.
Note: Selected System Organ Classes are recoded to aggregate medically similar SOCs.
Note: Selected Preferred Terms are recoded to aggregate medically similar PTs.
[a] Not applicable per CTCAE v4.03

Serious adverse event/deaths/other significant events

Serious adverse events

In the Sd group, 130 (60.7%) patients had at least 1 SAE. The most frequently reported SAEs in the Sd group (occurring in ≥5% of patients) were pneumonia (16 [7.5%] patients) and sepsis (13 [6.1%]

patients). Fifty-nine (27.6%) patients in the Sd group in the All MM Pool had at least 1 treatment-related SAE. The most frequently reported treatment-related SAEs in the Sd group (occurring in ≥2% of patients) were thrombocytopenia (6 [2.8%] patients); fatigue (5 [2.3%] patients); and confusional state, nausea, pneumonia, and dehydration (5 [2.3%] patients each).

Table 49 Serious Treatment-Emergent Adverse Events Occurring in ≥2% of Patients in the All MM Pool Overall and by Selected Selinexor Treatment Regimens within the All MM Pool

MedDRA System Organ Class MedDRA Preferred Term	All MM (N = 552) n (%)	S(80 mg)+d (N = 214) n (%)	KCP-330-012/STORM Part 2 (N = 123) n (%)	Other S±d (N = 71) n (%)
Blood and lymphatic system disorders				
Febrile neutropenia	17 (3.1)	4 (1.9)	0	5 (7.0)
Thrombocytopenia	16 (2.9)	10 (4.7)	3 (2.4)	2 (2.8)
Anaemia	13 (2.4)	7 (3.3)	4 (3.3)	1 (1.4)
Gastrointestinal disorders				
Nausea	11 (2.0)	5 (2.3)	2 (1.6)	1 (1.4)
General disorders and administration site conditions				
Pyrexia	15 (2.7)	6 (2.8)	3 (2.4)	5 (7.0)
Infections and infestations				
Pneumonia	46 (8.3)	16 (7.5)	14 (11.4)	12 (16.9)
Sepsis	22 (4.0)	13 (6.1)	12 (9.8)	3 (4.2)
Metabolism and nutrition disorders				
Dehydration	11 (2.0)	5 (2.3)	3 (2.4)	3 (4.2)
Renal and urinary disorders				
Acute kidney injury	16 (2.9)	8 (3.7)	3 (2.4)	3 (4.2)

Source: Table 14.3.3.4.2.1.2.1.1, CSR KPT-330-012 Table 14.3.3.1.1
(Database Cutoff Date: 2019-09-07)
Note: This table uses MedDRA version 22.0 for Study 012, and MedDRA version 20.1 for all other studies.
Note: Selected System Organ Classes are recoded to aggregate medically similar SOCs.
Note: Selected Preferred Terms are recoded to aggregate medically similar PTs.
Note: The All MM Pool includes all multiple myeloma patients dosed with selinexor (001, 012, 017, 023).
Note: The ≥2% threshold is based off of the All MM column.

Table 50 Serious Treatment-Emergent Adverse Events by Study Occurring in ⩾2% of Patients in the Total Safety Population

MedDRA System Organ Class MedDRA Preferred Term	001 (N = 285) n (%)	008 (N = 213) n (%)	009 (N = 254) n (%)	010 (N = 26) n (%)	012 (N = 202) n (%)	013 (N = 16) n (%)	017 (N = 132) n (%)	023 (N = 137) n (%)	Total (N = 1265) n (%)
Blood and lymphatic system disorders									
Febrile neutropenia	23 (8.1)	41 (19.2)	10 (3.9)	1 (3.8)	3 (1.5)	1 (6.3)	8 (6.1)	0	87 (6.9)
Thrombocytopenia	6 (2.1)	3 (1.4)	4 (1.6)	1 (3.8)	8 (4.0)	2 (12.5)	1 (0.8)	3 (2.2)	28 (2.2)
Anaemia	5 (1.8)	4 (1.9)	6 (2.4)	0	6 (3.0)	1 (6.3)	1 (0.8)	4 (2.9)	27 (2.1)
Gastrointestinal disorders									
Vomiting	7 (2.5)	7 (3.3)	9 (3.5)	0	4 (2.0)	0	1 (0.8)	4 (2.9)	32 (2.5)
Diarrhoea	2 (0.7)	10 (4.7)	6 (2.4)	0	4 (2.0)	1 (6.3)	2 (1.5)	3 (2.2)	28 (2.2)
General disorders and administration site conditions									
Pyrexia	9 (3.2)	12 (5.6)	10 (3.9)	1 (3.8)	6 (3.0)	1 (6.3)	4 (3.0)	0	43 (3.4)
Fatigue	7 (2.5)	9 (4.2)	3 (1.2)	1 (3.8)	6 (3.0)	1 (6.3)	0	2 (1.5)	29 (2.3)
Infections and infestations									
Pneumonia	24 (8.4)	29 (13.6)	17 (6.7)	2 (7.7)	16 (7.9)	1 (6.3)	12 (9.1)	8 (5.8)	109 (8.6)
Sepsis	22 (7.7)	19 (8.9)	15 (5.9)	3 (11.5)	13 (6.4)	0	4 (3.0)	2 (1.5)	78 (6.2)
Metabolism and nutrition disorders									
Dehydration	10 (3.5)	7 (3.3)	2 (0.8)	1 (3.8)	5 (2.5)	0	1 (0.8)	2 (1.5)	28 (2.2)
Respiratory, thoracic and mediastinal disorders									
Dyspnoea	3 (1.1)	6 (2.8)	7 (2.8)	2 (7.7)	4 (2.0)	1 (6.3)	2 (1.5)	2 (1.5)	27 (2.1)

Source: Table 14.3.3.4.3.1.1.1.3
(Database Cutoff Date: 2019-09-07)
Note: This table uses MedDRA version 22.0 for Study 012, and MedDRA version 20.1 for all other studies.
Note: Selected System Organ Classes are recoded to aggregate medically similar SOCs.
Note: Selected Preferred Terms are recoded to aggregate medically similar PTs.

Deaths

In the total safety population**,** 173 (13.7%) patients had at least 1 treatment-emergent fatal AE. The most frequent fatal TEAEs were sepsis (31 [2.5%] patients) and pneumonia (30 [2.4%] patients). The majority of cases of fatal pneumonia occurred in Study KCP-330-008/SOPRA (6.1%) in patients with relapsed/refractory AML, compared to the other studies. Other fatal TEAEs occurring in more than 2 patients included respiratory failure (9 [0.7%] patients), febrile neutropenia (8 [0.6%] patients; 7 patients from Study KCP-330-008/SOPRA), general physical health deterioration (7 [0.6%] patients), lung infection (7 [0.6%] patients), multiple organ dysfunction syndrome (7 [0.6%] patients), cerebral haemorrhage (5 [0.4%] patients), death (5 [0.4%] patients), malignant neoplasm progression (5 [0.4%] patients), intracranial haemorrhage (4 [0.3%] patients), and subdural haematoma (3 [0.2%] patients). All other fatal TEAEs occurred in 1 or 2 patients.

In study KPT-330-012 a total of 48 patients have died within 30 days of last dose of selinexor (20 in Part 1 and 28 in Part 2).

Out of 20 patients in Part 1, 12 patients were reported to have died due to disease progression and 8 patients were reported to have died due to TEAEs (1 patient had two TEAEs with a fatal outcome). The event terms included cardio-respiratory arrest (2), respiratory failure (1), influenza (1), multiple-organ dysfunction syndrome (1), ascites (1), plasma cell leukaemia (1), dyspnoea (1), and subdural haematoma (1). Of these only 1 event of subdural haematoma (Patient 0033-002) was assessed by the investigator as related to selinexor.

Out of a total 28 patients on Part 2 of the study, the cause of death was reported as disease progression in 15 patients, 12 patients were reported to have died due to a TEAE, and the cause of

death was not reported for 1 patient. Of the 12 patients who died due to a TEAE, 3 were assessed by the investigator as related to selinexor and 9 were assessed as not related by the investigator.

Table 51 TEAEs Leading to Death in Patients Treated with Sd, by SOC and PT - (Safety Analysis Population)

System Organ Class Preferred Term	Part 2 (N = 123) n (%)	Part 1 (N = 79) n (%)	Total (N = 202) n (%)
Patients with ≥ 1 TEAE	12 (9.8)	8 (10.1)	20 (9.9)
Cardiac disorders	**1 (0.8)**	**2 (2.5)**	**3 (1.5)**
Cardio-respiratory arrest	0	2 (2.5)	2 (1.0)
Cardiac disorder	1 (0.8)	0	1 (0.5)
General disorders and administration site conditions	**2 (1.6)**	**1 (1.3)**	**3 (1.5)**
Multiple organ dysfunction syndrome	1 (0.8)	1 (1.3)	2 (1.0)
Infections and infestations	**6 (4.9)**	**1 (1.3)**	**7 (3.5)**
Sepsis	4 (3.3)	0	4 (2.0)
Pneumonia	2 (1.6)	0	2 (1.0)
Influenza	0	1 (1.3)	1 (0.5)
Injury, poisoning, and procedural complications	**1 (0.8)**	**1 (1.3)**	**2 (1.0)**
Subdural hematoma	1 (0.8)	1 (1.3)	2 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**1 (1.3)**	**1 (0.5)**
Plasma cell leukaemia	0	1 (1.3)	1 (0.5)
Respiratory, thoracic, and mediastinal disorders	**2 (1.6)**	**2 (2.5)**	**4 (2.0)**
Dyspnoea	0	1 (1.3)	1 (0.5)
Pulmonary embolism	1 (0.8)	0	1 (0.5)
Respiratory arrest	1 (0.8)	0	1 (0.5)
Respiratory failure	0	1 (1.3)	1 (0.5)

Source Table 14.3.8.1.2.
Note: Selected System Organ Classes are recoded to aggregate medically similar SOCs.
Note: Selected Preferred Terms are recoded to aggregate medically similar PTs Note: Adverse Events are coded using MedDRA version 22.0. Patients are counted once within each system organ class and preferred term. Percentages are based on the number of all-treated patients in each treatment group. A treatment- emergent AE (TEAE) is defined as an AE that emerged or worsened in the period from date of first dose to 30 days after the date of last dose. The date of onset of the AE was used to determine treatment emergence.

Laboratory findings

Haematology

In the Sd group, the most frequently reported shifts from baseline to a worst on-study value ≥ Grade 3 were thrombocytopenia (144 [69.2%] patients), anaemia (102 [49%] patients), lymphocytopenia (93 [46.7%] patients), leukopenia (82 [39.4%] patients), and neutropenia (69 [33.5%] patients).

Clinical chemistry

In the Sd group, the most frequently reported shifts from baseline clinical chemistry parameters to a worst post-baseline value ≥ Grade 3 (occurring in ≥5% of patients) were hyponatraemia (64 [30.0%] patients), hyperglycaemia (27 [12.9%] patients), hypophosphataemia (21 [11.4%] patients), hypokalaemia (19 [8.9%] patients), increased creatinine (19 [8.9%] patients), and hyperlipasaemia (9 [5.1%] patients).

ECG

The ECG issue and the possible QTc interval concern is further commented in the PD section. Selinexor is not expected to cause clinically relevant QTc prolongation at the therapeutic dose concentrations of selinexor.

Safety in special populations

An analysis of safety data by age, sex or race did not identified clinically meaningful differences, although there were some imbalances in the incidence of certain AEs.

An increased frequency of nausea, anaemia, neutropenia and vomiting was reported in female patients compared to male patients. Infections were also more common in female than in male (61% vs 45.6%, respectively), mainly upper respiratory tract infections and urinary tract infections. Vision blurred was reported in 14% of patients in the Sd group; frequency was higher in women (23%) compared to men (6.1%).

An increased frequency of pneumonia and decreased appetite was also observed in patients ≥75 years. Regarding race, the small number of patients included in some of the subgroups makes difficult to draw conclusions.

Table 52 Summary of treatment-emergent adverse events by age and preferred term (STORM Part 2 Population)

MedDRA Terms	<65 years (N=60) n (%)	65 – 74 years (N=44) n (%)	75 – 84 years (N=18) n (%)	≥85 years (N=1) n (%)
Patients experiencing at least ≥1	60 (100.0)	44 (100.0)	18 (100.0)	1 (100.0)
TEAE	60 (100.0)	44 (100.0)	18 (100.0)	1 (100.0)
SAE	37 (61.7)	26 (59.1)	14 (77.8)	1 (100.0)
Fatal	4 (6.7)	4 (9.1)	4 (22.2)	0
Led to/ prolonging hospitalization	37 (61.7)	24 (54.5)	13 (72.2)	1 (100.0)
Life-threatening	0	3 (6.8)	0	0
Led to disability/ incapacity	1 (1.7)	0	0	0
Other medically significant	1 (1.7)	2 (4.5)	2 (11.1)	0
AE leading to drop-out	14 (23.3)	15 (34.1)	11 (61.1)	0
Psychiatric disorders	23 (38.3)	18 (40.9)	8 (44.4)	1 (100.0)
Nervous system disorders	29 (48.3)	22 (50.0)	11 (61.1)	1 (100.0)
Accidents and injuries	7 (11.7)	9 (20.5)	4 (22.2)	1 (100.0)
Cardiac disorders	5 (8.3)	5 (11.4)	2 (11.1)	0
Vascular disorders	4 (6.7)	10 (22.7)	3 (16.7)	0
Cerebrovascular disorders	0	0	0	0
Infections and infestations	35 (58.3)	20 (45.5)	14 (77.8)	1 (100.0)
Anticholinergic syndrome	28 (46.7)	27 (61.4)	11 (61.1)	1 (100.0)

MedDRA Terms	<65 years (N=60) n (%)	65 – 74 years (N=44) n (%)	75 – 84 years (N=18) n (%)	≥85 years (N=1) n (%)
Quality of life decreased[a]				
Fatigue	36 (60.0)	27 (61.4)	14 (77.8)	1 (100.0)
Decreased appetite	31 (51.7)	23 (52.3)	15 (83.3)	0
Diarrhoea	24 (40.0)	23 (52.3)	9 (50.0)	0
Nausea	41 (68.3)	33 (75.0)	14 (77.8)	0
Vomiting	23 (38.3)	20 (45.5)	4 (22.2)	0
Constipation	14 (23.3)	10 (22.7)	3 (16.7)	0
Factors leading to fracture[b]	18 (30.0)	16 (36.4)	6 (33.3)	1 (100.0)
Other[c]				
Hyponatraemia	18 (30.0)	19 (43.2)	7 (38.9)	1 (100.0)
Leukopenia	16 (26.7)	19 (43.2)	6 (33.3)	0
Dyspnoea	9 (15.0)	15 (34.1)	3 (16.7)	0
Asthenia	8 (13.3)	6 (13.6)	7 (38.9)	1 (100.0)
Fall	5 (8.3)	5 (11.4)	4 (22.2)	1 (100.0)
Confusional state	3 (5.0)	8 (18.2)	1 (5.6)	1 (100.0)
Oedema peripheral	3 (5.0)	6 (13.6)	4 (22.2)	0
Abdominal pain	3 (5.0)	7 (15.9)	2 (11.1)	0
Dysguesia	3 (5.0)	5 (11.4)	4 (22.2)	0
Hyperkalaemia	2 (3.3)	6 (13.6)	3 (16.7)	0
Hypomagnesaemia	2 (3.3)	7 (15.9)	1 (5.6)	0
General physical health deterioration	3 (5.0)	2 (4.5)	4 (22.2)	0
Hypercreatininaemia	3 (5.0)	3 (6.8)	3 (16.7)	0
Gait disturbance	1 (1.7)	2 (4.5)	4 (22.2)	0
Visual impairment	1 (1.7)	1 (2.3)	4 (22.2)	0
Neck pain	0	2 (4.5)	2 (11.1)	0

a There were no reports of "quality of life decreased". Therefore, those events that are commonly associated with selinexor that could impact a patient's quality of life has been included for this category

b Consists of the following terms: postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures.

c Preferred terms included under "Other" are those in which there is >10% difference across the <65 years, 65-74 years, and 75-84 years. As only 1 patient was 85 years of age or older, this group was not considered in this assessment.

Table 53 Summary of treatment-emergent adverse events by age and preferred term (ISS Pool 2 Population)

MedDRA Terms	<65 years (N=113) n (%)	65 – 74 years (N=78) n (%)	75 – 84 years (N=22) n (%)	≥85 years (N=1) n (%)
Patients experiencing at least ≥1	113 (100.0)	78 (100.0)	22 (100.0)	1 (100.0)
TEAE	113 (100.0)	78 (100.0)	22 (100.0)	1 (100.0)
SAE	66 (58.4)	47 (60.3)	16 (72.7)	1 (100.0)
Fatal	8 (7.1)	7 (9.0)	5 (22.7)	0
Led to/ prolonging hospitalization	65 (57.5)	41 (52.6)	15 (68.2)	1 (100.0)
Life-threatening	5 (4.4)	7 (9.0)	1 (4.5)	0
Led to disability/ incapacity	2 (1.8)	1 (1.3)	0	0
Other medically significant	1 (0.9)	4 (5.1)	2 (9.1)	0
AE leading to drop-out	27 (23.9)	23 (29.5)	12 (54.5)	0
Psychiatric disorders	46 (40.7)	25 (32.1)	10 (45.5)	1 (100.0)
Nervous system disorders	57 (50.4)	39 (50.0)	12 (54.5)	1 (100.0)
Accidents and injuries	13 (11.5)	18 (23.1)	4 (18.2)	1 (100.0)
Cardiac disorders	12 (10.6)	12 (15.4)	2 (9.1)	0
Vascular disorders	14 (12.4)	11 (14.1)	3 (13.6)	0
Cerebrovascular disorders	0	0	0	0
Infections and infestations	58 (51.3)	38 (48.7)	16 (72.7)	1 (100.0)
Anticholinergic syndrome	59 (52.2)	44 (56.4)	12 (54.5)	1 (100.0)
Quality of life decreased[a]				
Fatigue	79 (69.9)	49 (62.8)	14 (63.6)	1 (100.0)
Decreased appetite	59 (52.2)	43 (55.1)	17 (77.3)	0
Diarrhoea	49 (43.4)	38 (48.7)	12 (54.5)	0
Nausea	85 (75.2)	59 (75.6)	16 (72.7)	0
Vomiting	49 (43.4)	36 (46.2)	5 (22.7)	0
Constipation	28 (24.8)	20 (25.6)	3 (13.6)	0
Factors leading to fracture[b]	29 (25.7)	33 (42.3)	6 (27.3)	1 (100.0)
Other[c]				
Leukopenia	28 (24.8)	29 (37.2)	6 (27.3)	0
Dizziness	12 (10.6)	16 (20.5)	3 (13.6)	1 (100.0)
Asthenia	13 (11.5)	8 (10.3)	7 (31.8)	1 (100.0)
Pneumonia	13 (11.5)	6 (7.7)	7 (31.8)	0
Fall	6 (5.3)	10 (12.8)	4 (18.2)	1 (100.0)
Hypocalcaemia	8 (7.1)	7 (9.0)	4 (18.2)	0
Oedema peripheral	6 (5.3)	9 (11.5)	4 (18.2)	0
Hyperkalaemia	3 (2.7)	6 (7.7)	3 (13.6)	0
Gait disturbance	3 (2.7)	4 (5.1)	4 (18.2)	0
General physical health deterioration	3 (2.7)	2 (2.6)	4 (18.2)	0
Visual impairment	1 (0.9)	3 (3.8)	4 (18.2)	0

a There were no reports of "quality of life decreased". Therefore, those events that are commonly associated with selinexor that could impact a patient's quality of life has been included for this category

b Consists of the following terms: postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures.

c Preferred terms included under "Other" are those in which there is >10% difference across the <65 years, 65-74 years, and 75-84 years. As only 1 patient was 85 years of age or older, this group was not considered in this assessment.

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

No specific clinical studies assessing the effects of other drugs or extrinsic factors on selinexor were submitted.

Discontinuation due to adverse events

Of the 214 patients in the Sd group, 60 (28.0%) patients had at least 1 TEAE that led to the withdrawal of selinexor. The most frequently reported (occurring in ≥2% of patients) TEAEs leading to withdrawal of selinexor were fatigue and nausea (11 [5.1%] patients each), decreased appetite and decreased weight (7 [3.3%] patients each), and asthenia and thrombocytopenia (6 [2.8%] patients each).

Table 54 Treatment-Emergent Adverse Events Leading to Withdrawal from Selinexor Occurring in ≥1% of Patients in the All MM Pool Overall and by Selected Treatment Regimens within the All MM Pool

MedDRA Preferred Term	All MM (N = 552) n (%)	S(80 mg)+d (N = 214) n (%)	KCP-330-012/STORM Part 2 (N = 123) n (%)	Other S±d (N = 71) n (%)
Fatigue	20 (3.6)	11 (5.1)	6 (4.9)	4 (5.6)
Nausea	16 (2.9)	11 (5.1)	7 (5.7)	3 (4.2)
Decreased appetite	14 (2.5)	7 (3.3)	3 (2.4)	2 (2.8)
Thrombocytopenia	12 (2.2)	6 (2.8)	3 (2.4)	0
Weight decreased	8 (1.4)	7 (3.3)	5 (4.1)	1 (1.4)
Asthenia	7 (1.3)	6 (2.8)	5 (4.1)	0
Pneumonia	6 (1.1)	4 (1.9)	4 (3.3)	1 (1.4)
Vomiting	6 (1.1)	4 (1.9)	3 (2.4)	2 (2.8)

Source: Table 14.3.15.2.1.4, CSR KPT-330-012 Table 14.3.6.1.3
(Database Cutoff Date: 2019-09-07)
Note: This table uses MedDRA version 22.0 for Study 012, and MedDRA version 20.1 for all other studies.
Note: Selected Preferred Terms are recoded to aggregate medically similar PTs.
Note: The All MM Pool includes all multiple myeloma patients dosed with selinexor (001, 012, 017, 023).
Note: The ≥1% threshold is based off of the All MM column.

Total Safety Population

Of the 1265 patients in the Total Safety Population, 309 (24.4%) patients had at least 1 TEAE that led to the withdrawal of selinexor. The most frequently reported (occurring in ≥2% of patients) TEAEs leading to withdrawal of selinexor were fatigue (42 [3.3%] patients), thrombocytopenia (32 [2.5%] patients), decreased appetite (26 [2.1%] patients), and pneumonia (25 [2.0%] patients).

Table 55 Treatment-Emergent Adverse Events Leading to Withdrawal from Selinexor Occurring in ≥1% of Patients by Study in the Total Safety Population

MedDRA Preferred Term	001 (N = 285) n (%)	008 (N = 213) n (%)	009 (N = 254) n (%)	010 (N = 26) n (%)	012 (N = 202) n (%)	013 (N = 16) n (%)	017 (N = 132) n (%)	023 (N = 137) n (%)	Total (N = 1265) n (%)
Fatigue	12 (4.2)	6 (2.8)	5 (2.0)	1 (3.8)	11 (5.4)	2 (12.5)	4 (3.0)	1 (0.7)	42 (3.3)
Thrombocytopenia	2 (0.7)	1 (0.5)	13 (5.1)	1 (3.8)	6 (3.0)	1 (6.3)	3 (2.3)	3 (2.2)	30 (2.4)
Decreased appetite	5 (1.8)	4 (1.9)	3 (1.2)	0	7 (3.5)	3 (18.8)	3 (2.3)	2 (1.5)	27 (2.1)
Pneumonia	0	11 (5.2)	7 (2.8)	1 (3.8)	4 (2.0)	0	1 (0.8)	1 (0.7)	25 (2.0)
Nausea	5 (1.8)	2 (0.9)	4 (1.6)	0	10 (5.0)	1 (6.3)	1 (0.8)	1 (0.7)	24 (1.9)
Sepsis	0	11 (5.2)	5 (2.0)	1 (3.8)	3 (1.5)	0	0	0	20 (1.6)
Febrile neutropenia	2 (0.7)	12 (5.6)	1 (0.4)	1 (3.8)	0	0	1 (0.8)	0	17 (1.3)

Source: Table 14.3.15.2.3.1
(Database Cutoff Date: 2019-09-07)
Note: This table uses MedDRA version 20.1.
Note: Selected Preferred Terms are recoded to aggregate medically similar PTs.
Note: The ≥1% threshold is based off of the total column.

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

The safety profile of selinexor is based on data from 1265 patients with advanced haematological malignancies (MM, AML, NHL) treated with selinexor in 8 clinical trials, most of them are Phase 1 or Phase 2 uncontrolled studies (only data from an ongoing Phase 3 study have been included in the integrated summary of safety analysis), in which selinexor was administered in different dosing regimens and combinations. This application is mainly based on two studies of the above-mentioned, the KCP-330-012 study, which is the pivotal study, and the KCP-330-001 study, a dose-escalation Phase 1 study. In total, 214 patients received selinexor at the proposed dosing regimen (80 mg twice weekly or 45 mg/m^2 combined with low dose dexamethasone), for the treatment of RRMM. Study KCP-330-012 included 202 patients with heavily pre-treated MM, of whom 83 patients included in Part 2 of the study represent the penta-refractory intended target population (i.e. refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide and daratumumab). Additionally, 12 patients (with MM previously treated with, and relapsed or refractory to, ≥3 prior regimens) from study KCP-330-001 have been included in the safety dataset. Safety data of these 1256 patients have been presented as pooled data. Data of the 214 patients treated with selinexor+dexamethasone (Sd Pool) is considered the main safety dataset. However, the total safety population has been taken into account to obtain a broader perspective of the safety profile of selinexor.

The absence of a control arm in study KCP-330-012/STORM is one of the limitations of this safety dataset, especially in this setting of a heavily pre-treated population, as it makes difficult to establish to what extent adverse events reported in patients treated with selinexor could be related to the study treatment or on the contrary they were associated with the underlying disease and previous treatment received.

In the Sd Pool the median duration of therapy was 8.5 weeks (range: 1, 76), with a median of doses received of 11 (range: 1, 135). Duration of exposure was ≥24 weeks for 31 (14.5%) patients, of whom

4 (2.3%) received selinexor for 48 weeks or more. Therefore, rare adverse events could be underestimated or even not estimated.

Overall, selinexor tolerability appears to be low, according to the high number of patients that required dose modification (dose reduction and/or dose interruption) due to AEs (73.8%). At the database cut-off date (7 September 2019), all patients had discontinued study treatment, most of them due to disease progression (56.1%). However, it is of concern the high number of patients that discontinued treatment due to adverse events. In Part 2 of study STORM, 39 (31.7%) patients discontinued study treatment due to adverse events, being nausea (7 patients; 17.9%), fatigue (6 patients; 15.4%), weight decreased (5 patients; 12.8%) and asthenia (5 patients; 12.8%) the leading causes.

Per protocol, patients included in Part 2 of study KCP-330-012 received a dose of 80 mg twice weekly (days 1 and 3 of each week) continuously in 4-weeks cycles combined with dexamethasone 20 mg twice-weekly (in Part 1 of the study, selinexor was administered twice weekly for 3 weeks of each 4-weeks cycle). However, in select cases, after 2 cycles of treatment, the selinexor dose could be increased to 100 mg (<70 mg/m^2) twice weekly (after discussion with the Sponsor) based on efficacy considerations. There were only two patients who had their doses increased to 100 mg BIW and two additional patients that received 100 mg but once a week instead of twice a week. The proposed dose for selinexor is mainly based on study KCP-330-001, in which 81 patients with MM were included; 12 of these 81 patients received selinexor 45 mg/m^2 in combination with 20 dexamethasone twice weekly. According to the applicant, the selected dose showed anti-MM activity with a better safety profile than higher doses used (60 mg/m^2).

Adverse events

All patients in the Sd Pool experienced an AE and most of them were considered treatment-related (98.6%). The most commonly reported (≥30%) AEs were nausea (74.8%), thrombocytopenia (75.2%), fatigue (66.4%), anaemia (60.3%), decreased appetite (56.1%), weight decreased (49.1%), diarrhoea (47.2%), vomiting (42.5%), hyponatraemia (39.7%) and neutropenia (36.4%) (SmPC, section 4.8)

Overall, the safety profile was comparable with that observed for the total safety population (n=1265), although the incidence of these commonly reported AEs was higher in the Sd Pool, specially weight decreased (28.5%) and anaemia (41.7%).

With regard to grade ≥3 AEs, they were reported in 99% of patients. The most frequently reported grade ≥3 AEs were thrombocytopenia (65%), anaemia (43.9%), hyponatraemia (23.4%), neutropenia (22.9%), fatigue (20.1%), leukopenia (14.5%) and lymphopenia (10.7%) reported in more than 10% of patients. Thrombocytopenia was also the most common grade 4 AE (SmPC, section 4.8).

Serious adverse events (SAEs)

SAEs were reported by 60.7% of patients. Overall, pneumonia and sepsis were the most common SAEs reported (16 [7.5%] and 13 [6.1%], respectively). Nearly half of SAEs (27.6%) were considered by the investigator as treatment-related, being thrombocytopenia (4.7%), fatigue (2.8%), pneumonia, dehydration and hyponatraemia (2.3% each) the most frequent treatment-related SAEs (SmPC, section 4.8).

In the overall population treated with selinexor, either as monotherapy (±dexa) or in combination, pneumonia and sepsis were also the most commonly reported SAEs.

Deaths

In the study KPT-330-012 a total of 48 patients died within 30 days of last dose of selinexor (20 in Part 1 and 28 in Part 2 – Cut-off date7 September 2019). Disease progression was the cause of death in 27

patients, whereas in 20 (9.9%) patients the cause of death was a fatal AE. Sepsis (4 [2.0%]), subdural haematoma, cardio-respiratory arrest and pneumonia, (2 [1.0%], each) were the main causes of deaths. The listed causes of death are commonly seen in heavily treated RRMM patients. There were 12 deaths in STORM/Part 2 of which 6 were under the SOC Infections and Infestations; as this is not uncommon in this heavily treated population the contribution of selinexor is difficult to assess.

In the total safety population (n=1265), sepsis (31 [2.5%]) and pneumonia (30 [2.4%) were the main fatal AEs. There were also approximately 1% of deaths related to haemorrhagic AEs.

Adverse events of special interest (AEOSIs)

Haematological adverse events were commonly reported in patients treated with selinexor in clinical trials. Of these, thrombocytopenia was the most commonly reported AE. In the Sd Pool it was the most frequent grade 4 adverse event reported in patients treated with selinexor (40.7%) and one of the leading causes to treatment discontinuation due to AEs (6 [2.8%] patients). In study KPT-330-012 around 18% of the patients who had AEs of thrombocytopenia received supportive care within 5 days. Thrombopoietin receptor agonists such as romiplostim, could also be used. Haemorrhagic AEs could be related to thrombocytopenia as the cause. However, despite the high incidence of grade ≥ 3 thrombocytopenia AEs with selinexor, the incidence of bleeding events was relatively low. In study KPT-330-012 of the 124 patients with grade ≥3 thrombocytopenia, 5 (4%) patients had a concomitant grade ≥ 3 or serious bleeding event, one of them fatal (subdural haematoma). Thrombocytopenia can be managed with dose interruptions, modifications, platelet transfusions, and/or other treatments as clinically indicated (SmPC, section 4.4). Other haematological AEOSI were neutropenia and anaemia. Patients with neutropenia could receive granulocyte colony stimulating factors (GCSF) (SmPC, section 4.4). The incidence of febrile neutropenia in patient treated with selinexor for MM was low.

Gastrointestinal AEs were frequently reported in selinexor clinical trials, mainly diarrhoea, nausea and vomiting. Most of the events of nausea, vomiting and diarrhoea were grade 1 or grade 2 and no fatal AEs were reported. In the Sd Pool 15 (7%) patients discontinued treatment due to nausea/vomiting and 2 (0.9%) patients due to diarrhoea. In addition, adverse events such as fatigue, decreased appetite and weight decreased were also commonly reported in patients treated with selinexor and have been included as important identified risks in the RMP. The majority of these AEs were grade 1 or grade 2 and incidence of SAEs was low. However, rates of treatment discontinuation due to these AEs is of concern. In the Sd Pool (n=214), fatigue, decreased appetite, weigh decreased and asthenia accounts for approximately 50% of selinexor treatment discontinuations due to AEs. A similar pattern is observed in study KCP-330-008, a randomised, phase 2 study in elderly patients (≥60 years) with relapsed or refractory AML, in which the incidence of these AEs was also higher in patients treated with selinexor compared to those that received Physician´s choice. Furthermore, a reduced food intake leading to weight loss was also observed in studies performed in animals.

The exact mechanism associated to these AEs (i.e., nausea, vomiting, fatigue, decreased appetite, weight decreased) is not clear but it is considered they might be mediated by CNS toxicity and not due to peripheral effects. Other XPO-1 inhibitors have been related to adverse drug reactions such as anorexia, nausea, fatigue, and weight loss (Newlands ES 1996; Hing 2016), considered all of them as a class effect. Adverse events of fatigue, anorexia and weight loss reported with XPO-1 inhibitors have been postulated to be related to their ability to cross the BBB (Hing 2016).

Nervous system disorders such as confusional state and dizziness are AEs of special interest reported in patients treated with selinexor. The exact mechanism of action associated with these AEs is unknown and although other confounding factors were present, a causal association between selinexor and AEs of confusional state and dizziness cannot be ruled out. In the Sd Pool, confusional state was reported in 38 (17.8%) patients, of which in 13 (6.1%) patients were considered as SAE and there

were 5 (2.3%) patients that discontinued selinexor treatment due to confusional state. Dizziness was reported in 16% of patients. Additionally, 3 cases of acute cerebellar syndrome (ACS) have been reported in selinexor clinical trials. One of the cases was reported in a patient with pancreatic cancer and the other two in paediatric patients with AML. According to the applicant these patients were receiving higher doses (85 mg/m^2 adult patient and 70 mg/m^2 in children) of selinexor and all cases were reversible. No events of ACS have been reported in the Sd Pool. However, central nervous toxicity (i.e. necrosis of cerebellar granular cells) has been observed in non-clinical trials. Therefore, ACS is considered an important potential risk of selinexor (see Risk Management Plan).

Hyponatraemia was frequently reported. In the Sd Pool 23.8% of patients experienced hyponatraemia of grade ≥3 (two of them of grade 4), although in general it was manageable. The mechanism by which selinexor causes hyponatraemia has not been fully clarified. According to the applicant it seems to be related to (renal) sodium loss, rather than other causes such as SIADH or a more general diuretic effect.

Among patients treated with selinexor in clinical trials, 4 cases of TLS have been reported (1 in the Sd Pool). The association of selinexor and TLS is not completely clear; however, considering it is related to a significant morbidity, the applicant has included TLS as an important potential risk in the RMP.

Infections and eye disorders were also included as AEs of special interest.

Safety related to drug-drug interactions

Clinical experience of selinexor with a large variety of co-administered drugs suggests a lack of DDI potential of selinexor. See pharmacology section for further information.

Laboratory findings

Overall, the laboratory findings are reflecting the safety profile of this drug. Thrombocytopenia, anaemia, neutropenia, leukopenia and hyponatraemia were the most commonly reported.

Shifts commonly observed in other clinical chemistry parameters to a worst post-baseline value (grade ≥3) in the Sd Pool were hyperglycaemia (12.9%), hypophosphataemia (11.4%), hypokalaemia (8.9%) and creatinine increased (8.9%).

ALT and AST increased have been reported in patients treated with selinexor (26.8% and 25.4%, respectively). Most of them were grade 1 or grade 2 (shifts from baseline to a post-baseline value grade ≥3 was reported in 2.8% and 1.9% patients, respectively). One patient had a hepatic grade 4 SAE (liver transaminases just below 4000 U/L) considered "probably or definitely related" (it took about 25 days for this to resolve). One reduced dose of 60 mg selinexor was given after this and ALT/AST were normal one week after this, but then treatment was apparently discontinued.

Lypase and amylase increased have been reported in 15.4% and 15.8% of patients in Sd Pool, respectively, of which 5.1% and 2.3% were shifts to grade 3 or 4. Moreover, two events of pancreatitis have been reported among patients treated with selinexor; one in study STORM, which was considered by the investigator treatment-related and the other in study 008, in patients with AML.

Subgroups of special interest

An analysis of safety data by age, sex or race did not identified clinically meaningful differences, although there were some imbalances in the incidence of certain AEs. An increased frequency of nausea, anaemia, neutropenia and vomiting was reported in female patients compared to male patients. Infections were also more common in female than in male (61% vs 45.6%, respectively), mainly upper respiratory tract infections and urinary tract infections. Blurred vision was reported in 14% of patients in the Sd group; frequency was higher in women (23%) compared to men (6.1%).

However, considering all the available data, a higher risk of blurred vision in women compared to men due to selinexor treatment is not expected.

An increased frequency of pneumonia and decreased appetite was also observed in patients ≥75 years. Regarding race, the small number of patients included in some of the subgroups makes difficult to draw conclusions.

The median age at enrolment of the Sd group and STORM/Part 2 is 64.0 and 65.2 years, respectively. Given a median time since diagnosis of 6 years, these patients may not represent the general MM population, as the median age *at diagnosis* in the general population is around 72 years. The low ECOG performance score (ECOG 2; 9.3%, the rest had ECOG 0 or 1) in this heavily treated population most likely reflects the relatively young study population. Selinexor usage in a real-life cohort of MM patients, which on average are older than in the study, could potentially lead to even more adverse events including severe and serious.

It should be noticed that at least seven cases of selinexor overdose have been reported in clinical trials, most of them in study KCP-330-023 (BOSTON), in which selinexor is administered at a dose of 100 mg once a week. Considering the toxicity associated to selinexor and the potential risk of medication errors (i.e. taking daily instead of twice a week), medication errors has been included as an important potential risk (see Risk Management Plan).

Selinexor may cause foetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. Males and females of reproductive potential should be advised to use highly effective contraception during treatment with selinexor. There are no data on the presence of selinexor in human milk or its effects on breastfed infants or on milk production. Due to the potential for serious adverse reactions in breastfed infants from selinexor, it is advised that lactating women not breastfeed during selinexor treatment or for 1 week following the final dose (SmPC, sections 4.4, 4.6 and 5.3).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional expert consultations

A Scientific Advisory Group in Oncology (SAG-O) was asked to provide their view on the two following questions:

1. Do available data indicate clinically meaningful efficacy in the sought indication?
2. Is the observed safety profile of selinexor acceptable in the proposed target population?

This SAG-O meeting took place on 30th November 2020. The final minutes on the question 2 are included below. For the minutes on question 1, please see section 2.5.3. Discussion on Clinical Efficacy.

Is the observed safety profile of selinexor acceptable in the proposed target population?

The observed toxicity in the STORM study was clinically significant, including frequent severe haematological toxicity, especially thrombocytopenia and anaemia, and frequent severe nausea and vomiting, and fatigue. However, this level of toxicity is not considered exceptional in this advanced haematological malignancy setting, and generally manageable with adequate monitoring and dose adjustment or discontinuation.

Optimal risk minimisation measures in terms of dose modifications and supportive care should be implemented, as well as monitoring of toxicity in the real-life setting. The claim that such measures are

effective in the post-marketing data available to the company should be explored to confirm the appropriateness of current risk minimisation measures.

In conclusion, the safety profile is acceptable taking into consideration other treatments in this setting, and well-characterised to allow informed individual clinical benefit-risk decisions.

Additional safety data needed in the context of a conditional MA

Additional comparative safety data from the confirmatory study BOSTON, a phase 3, randomised, active comparator-controlled, open-label, multicentre (sites worldwide) study to compare the efficacy and assess the safety of selinexor plus bortezomib plus low-dose dexamethasone (SVd) versus bortezomib plus low dose dexamethasone (Vd) in ~364 adult patients with RRMM who have received 1 to 3 prior anti-MM regimens (data cut-off February 2021) will be provided as part of the specific obligation in order to fulfil a CMA and will allow a better characterisation and contextualisation of the safety profile of selinexor.

2.6.2. Conclusions on the clinical safety

Overall, the tolerability of selinexor appears to be low. However, even if the toxicity of selinexor is not negligible, the safety profile in the target population can be considered generally manageable with adequate monitoring and dose adjustment or discontinuation. The fact that the safety profile in the penta-refractory population was consistent with the safety for the whole population in STORM Part 2 (n=123) concerning all AEs, SAEs and discontinuations due to AEs, with no new safety signals having been observed, is reassuring, since these patients are the most heavily pre-treated patients in the whole population included in the STORM study.

The safety has been considered sufficiently characterised in the context of a conditional MA. Additional data from the BOSTON study, i.e., a phase 3, randomised, active comparator-controlled, open-label, multicentre (sites worldwide) study to compare the efficacy and assess the safety of selinexor plus bortezomib plus low-dose dexamethasone (SVd) versus bortezomib plus low dose dexamethasone (Vd) in ~402 adult patients with RRMM who have received 1 to 3 prior anti-MM regimens will be provided in support of the overall safety profile of selinexor.

The CHMP considers the following measure necessary to address the missing safety data in the context of a conditional MA:

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 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.

2.7. Risk Management Plan

Safety concerns

Table 56 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	Tumour lysis syndrome Acute cerebellar syndrome Medication error
Missing information	Use in patients with severe renal impairment Use in patients with severe hepatic impairment

Pharmacovigilance plan

No additional Pharmacovigilance Activities are ongoing or planned at this point.

Risk minimisation measures

Table 57 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Safety concern 1: Thrombocytopenia and Bleeding	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8, PIL sections 2 and 4 SmPC section 4.2 where information on clinical measures for different grades of thrombocytopenia are described and section 4.4 and PIL section 2 where risk warnings are included. Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none proposed

Safety concern 2: Severe Infections due to Neutropenia	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8, PIL sections 2 and 4 SmPC section 4.2 where information on clinical measures for different grades of neutropenia are described and section 4.4 and PIL section 2 where risk warnings are included. Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none proposed
Safety concern 3: Fatigue	Routine risk minimisation measures: SmPC sections 4.2, , 4.7, 4.8 and PIL sections 2 and 4 SmPC section 4.2 where information on clinical measures for different grades of fatigue are described and section 4.4 and PIL section 2 where risk warnings are included. Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none proposed
Safety concerns 4 and 5: Decreased appetite and Weight decreased	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8, PIL sections 2 and 4 SmPC section 4.2 where information on clinical measures for different grades of decreased appetite and weight are described and section 4.4 and PIL section 2 where risk warnings are included. Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none proposed
Safety concern 6: Hyponatraemia	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8, PIL sections 2 and 4 SmPC section 4.2 where information on clinical measures for different grades of hyponatraemia are described and section 4.4 and PIL section 2 where risk warnings are included. Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none proposed

Safety concern 3: Fatigue	Routine risk minimisation measures: SmPC sections 4.2, , 4.7, 4.8 and PIL sections 2 and 4 SmPC section 4.2 where information on clinical measures for different grades of fatigue are described and section 4.4 and PIL section 2 where risk warnings are included. Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none proposed
Safety concerns 4 and 5: Decreased appetite and Weight decreased	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8, PIL sections 2 and 4 SmPC section 4.2 where information on clinical measures for different grades of decreased appetite and weight are described and section 4.4 and PIL section 2 where risk warnings are included. Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none proposed
Safety concern 6: Hyponatraemia	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8, PIL sections 2 and 4 SmPC section 4.2 where information on clinical measures for different grades of hyponatraemia are described and section 4.4 and PIL section 2 where risk warnings are included. Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none proposed
Safety concern 7: Confusional state	Routine risk minimisation measures: SmPC sections 4.4, 4.7, 4.8, PIL sections 2 and 4 SmPC section 4.4 and section 4.7 and PIL section 2 where risk warnings are included. Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none proposed

Safety concern 8: Tumour lysis syndrome	Routine risk minimisation measures: SmPC sections 4.4, 4.8 and PIL section 4 where risk warnings are included. Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none proposed
Safety concern 9: Acute cerebellar syndrome	Routine risk minimisation measures: none. Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none proposed
Safety concern 10: Medication error	Routine risk communication measure: Labelling and SmPC section 4.9 Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none proposed
Safety concern 11: Use in patients with severe renal impairment	Routine risk minimisation measures: SmPC section 5.2 where information on the missing information is provided. Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none proposed
Safety concern 12: Use in patients with severe hepatic impairment	Routine risk minimisation measures: SmPC section 5.2 where information on the missing information is provided. Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none proposed

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 03.07.2019. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of selinexor with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers selinexor to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Nexpovio (selinexor) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU
- It is approved under a conditional marketing authorisation [REG Art 14-a]

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Nexpovio, in combination with dexamethasone, is indicated 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.

3.1.2. Available therapies and unmet medical need

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 (IMiDs, such as thalidomide, lenalidomide and pomalidomide), monoclonal antibodies (mAbs, such as daratumumab, isatuximab and elotuzumab) and the histone deacetylase inhibitor panobinostat. There is a clear unmet medical need for new therapies because the treatment options are very limited and their median overall survival is around 3-5 months.

With the approval of daratumumab and its wide use in combinations in earlier lines of MM treatment, a new population of patients is created who have become refractory to all available agents (including daratumumab). This population can be referred to as triple-class refractory MM and it encompasses those patients with disease refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 mAb.

Penta-exposed MM is defined as MM previously treated with bortezomib, carfilzomib, lenalidomide, pomalidomide, and an anti-CD38 monoclonal antibody (mAb; either daratumumab or isatuximab).

Penta refractory MM has been defined as disease refractory to prior treatment with at least two proteasome inhibitors (PIs; bortezomib and carfilzomib), two immunomodulatory drugs (IMiDs; lenalidomide and pomalidomide), and one anti-CD38 mAb (daratumumab or isatuximab).

Although survival outcomes for patients with multiple myeloma (MM) have significantly improved over the past 2 decades due primarily to the introduction of novel classes of drugs, myeloma cells invariably acquire resistance, and nearly all patients develop disease that is refractory to the available therapies. Therefore, development of therapies with new mechanisms of action to overcome drug resistance would be important to address unmet medical needs in heavily pre-treated population.

3.1.3. Main clinical studies

The clinical package of Nexpovio was primarily supported by data from a Phase 2, multicentre, single-arm, open-label study designed to evaluate the efficacy and safety of selinexor in patients with penta-exposed, triple-class refractory MM (Study KCP-330-012/STORM, part 2). STORM Part 2 required patients to have measurable disease per International Myeloma Working Group (IMWG) criteria, have previously received three or more antimyeloma treatment regimens including an alkylating agent, glucocorticoids, bortezomib,

carfilzomib, lenalidomide, pomalidomide, and an anti-CD38 monoclonal antibody; and whose myeloma was documented to be refractory to glucocorticoids, a proteasome inhibitor, an immunomodulatory agent, an anti-CD38 monoclonal antibody, and to the last line of therapy. Patients had to have an ECOG performance status score ≤2, adequate hepatic, renal and haematopoietic function. Systemic light chain amyloidosis, active central nervous system myeloma, peripheral neuropathy of grade 3 or higher, or painful neuropathy of grade 2 or higher were exclusion criteria.

Patients were treated with 80 mg selinexor in combination with 20 mg dexamethasone on Days 1 and 3 of every week. Treatment continued until disease progression, death or unacceptable toxicity.

Part 1 of the KCP-330-012/STORM study (supportive study) included both patients with quad-exposed MM, double-class refractory MM as well as a subset with penta-exposed, triple-class refractory MM.

3.2. Favourable effects

For patients treated in Part 2 of STORM (pivotal study of this application)

- The **ORR per IRC** was 25.3 % (95% CI: 16.3, 36), which included 1 (1.2%) patient with an sCR/CR, 4 (4.8%) patients with a VGPR, and 16 (19.3%) patients with a PR; 10 (12.0%) patients had MR, 32 (38.6%) patients had SD, and 20 (24.1%) patients had PD/NE. The CBR was 37.3% (95% CI: 27.0, 48.7), which included all patients with an MR or better. The median time to response of PR or better was 3.9 weeks (range: 1-10).
- For patients with a response, the median **DoR per IRC** was 3.8 months (95% CI: 2.3, 10.8).
- The median **OS** was 8.4 months (95% CI: 5.9, 11.2)

For patients treated in Part 1 (supportive data)

- the **ORR per IRC** was 20.3% (95% CI: 12.0, 30.8), which included 4 (5.1%) patients with VGPR, and 12 (15.2%) patients with a PR; 9 (11.4%) of patients had MR, 30 (38.0%) patients had SD, and 24 (30.4%) patients had PD/NE. The median time to response of PR or better was 4.1 weeks (range: 2-8).
- For patients with a response, the median **DOR per IRC** was 6.2 months (95% CI: 3.6, 9.8).
- The median **OS** was 9.3 months (95% CI: 5.8, 11.3).

3.3. Uncertainties and limitations about favourable effects

The major uncertainty in evaluating the above results is due to the single arm design and lack of a comparator in the STORM study part 2. ORR as a primary endpoint is acceptable from a regulatory perspective, but the design of the study hinders an appropriate estimation of the actual benefit in terms of how the observed antitumour activity translates into an effect on time to event long term endpoints.

Further, the single arm design does not allow to isolate the contribution of the two components of the combination. Of note, based in study KCP-330-001, none of the patients exposed to selinexor in monotherapy obtained a response, only MR and SD were achieved. With regards to the activity of dexamethasone there are some reports in the literature showing that the use of high dose

dexamethasone could provide response rates of about 20% in patients with 1-3 prior therapies (Richardson 2005, Weber 2007) including also the pomalidomide study (Lancet Oncology, 2013) where an ORR of 10% was demonstrated in patients treated with high dose dexamethasone in patients having received a median number of prior therapies of 5. The only recent study where a low dose of dexamethasone was used as monotherapy in multiple myeloma corresponds to that conducted with plitidepsin, i.e. Study APL-C-001-09 (ADMYRE). In that study, plitidepsin in combination with dexamethasone vs. dexamethasone alone in patients with relapsed/refractory multiple myeloma was studied. Patients had a median of 4 lines of previous systemic therapies. The ORR in the dexamethasone arm (40 mg orally on Day 1, 8, 15 and 22 q4wk) was 1.2 %. These data contribute to alleviate the concerns that the effect observed with selinexor in combination with low dose dexamethasone could be mainly driven by the dexamethasone component.

Although ORR and DoR can be considered relevant endpoints to conclude on an effect likely to translate into clinically meaningful benefit in the proposed treatment setting, there is no comparison of PFS and OS in this patient population to other options.

As expected the median OS decreased with age. Median OS in the penta-refractory targeted population was 8.4 months (95% CI: 5.9; 11.2) with a longer OS for patients having a response of PR or better. However OS data are to be carefully interpreted in the context of a single arm trial. There is a need to further quantify the efficacy of selinexor in a comparative trial (Annex II.E).

3.4. Unfavourable effects

This application is mainly based on study KPT-330-012, a phase 2 study, which included 202 patients. Additionally, 12 patients from study KPT-330-001 who received Sd at the proposed dosing regimen have been included in the safety assessment. Altogether, 214 patients have been treated with selinexor 80 mg administered in combination with dexamethasone 20 mg twice weekly.

Overall the most commonly reported AEs in the Sd group (which included patients from the pivotal study KPT-330-012 + 12 patients from study KPT-330-001) were nausea (74.8%), thrombocytopenia (75.2%), fatigue (66.4%), anaemia (60.3%), decreased appetite (56.1%), weight decreased (49.1%), diarrhoea (47.2%), vomiting (42.5%), hyponatraemia (39.7%) and neutropenia (36.4%). All patients (100%) experienced an AE and most of the AEs were considered treatment-related (98.6%).

Grade ≥3 AEs were reported by 99% of patients. The most frequently reported grade ≥3 AEs were thrombocytopenia (65%), anaemia (43.9%), hyponatraemia (23.4%), neutropenia (22.9%), fatigue (20.1%), leukopenia (14.5%) and lymphopenia (10.7%) reported in more than 10% of patients. Thrombocytopenia was also the most common grade 4 AE, reported in 38.3% of patients.

SAEs were reported by 60.7% of patients. Sepsis and pneumonia were the most common SAEs (13 [6.1%] and 16 [7.5%], respectively). Nearly half of SAEs (27.6%) were considered by the investigator as treatment-related, being thrombocytopenia (3.3%), fatigue (2.8%), pneumonia, dehydration and hyponatraemia (2.3% each) the most frequent treatment-related SAEs (SmPC, section 4.8).

With regard to deaths, in study KPT-330-012 a total of 48 patients died within 30 days of last dose of selinexor (20 in Part 1 and 28 in Part 2). Disease progression was the cause of death in 27 patients, whereas in 20 (9.9%) patients the cause of death was a fatal AE. Sepsis (4 [2.0%]), subdural haematoma, cardio-respiratory arrest and pneumonia, (2 [1.0%], each) were the main causes of deaths. In the Sd group, 60 (28.0%) patients discontinued study treatment due to AEs. Fatigue (11 [5.1%]),

nausea (11 [18.3%]), weight decreased and decreased appetite (7 [11.7%], each) and asthenia and thrombocytopenia (6 [10%], each) were the main adverse events that led to treatment discontinuation. Additionally, 73.8% of patients required dose modifications (i.e. dose reductions and/or dose interruptions).

3.5. Uncertainties and limitations about unfavourable effects

The absence of a control arm is one of the main limitations of this safety dataset, especially in this setting of a heavily pre-treated population, as it makes difficult to establish to what extent adverse events reported in patients treated with selinexor could be related to the study treatment or on the contrary they were associated with the underlying disease and previous treatment received.

Furthermore, median treatment duration in the Sd group was of only 8.5 weeks (range: 1, 76), with a median of doses received of 11 (range: 1,135). Therefore, rare adverse events could be underestimated or even not estimated.

Adverse events such as fatigue, asthenia, nausea, decreased appetite and weight decreased were frequently reported in selinexor clinical trials and are among the leading causes for treatment discontinuation. Moreover, this is in line with non-clinical data, where reduced food intake and weight loss were the main side effects observed. The exact mechanism associated to these AEs is not known.

Moreover, nervous system disorders such as confusional status and dizziness were AEs of special interest reported in patients treated with selinexor. Additionally, 3 cases of acute cerebellar syndrome have been reported in selinexor clinical trials (one in a patient with pancreatic cancer and the other two in paediatric patients with AML). Despite the applicant states the 3 cases were reported in patients receiving higher doses of selinexor, additional monitoring of this adverse event is deemed necessary.

Submission of results from the confirmatory KCP-330-023/BOSTON study: A Phase 3 Randomized, Controlled, Open-label Study of Selinexor, Bortezomib, and Dexamethasone (SVd) versus Bortezomib and Dexamethasone (Vd) in Patients with Relapsed or Refractory Multiple Myeloma (RRMM) will provide additional data to evaluate the clinical significance of these events (see Annex II and RMP).

3.6. Effects Table

Table 58 Effects Table for Nexpovio in multiple myeloma patients whose disease is penta-refractory (data cut-off: 07 Sept 2019)

Effect	Short Description	Unit	Treatment	Result	Uncertainties/ Strength of evidence	References
Favourable Effects						

Effect	Short Description	Unit	Treatment	Result	Uncertainties/ Strength of evidence	References
ORR (N=83)	Percentage of patients who achieved a confirmed partial response (PR) or better (i.e., PR, VGPR, CR, or sCR), as assessed by the IRC, during or after the study treatment, before documented disease progression or initiating a new MM treatment.	n (%)	Selinexor 80 mg PO plus low-dose dexamethasone 20 mg PO (Sd) on Days 1 and 3 twice weekly	21 (25.3)	There seems to be no single agent activity of selinexor alone in RRMM (KCP-330-001) and it is not possible to isolate the treatment effect of selinexor vs. dexamethasone. The discontinuation rate in the STORM study due to adverse events remains high in comparison to other studies such as pomalidomide or daratumumab. 95% IC (16.3,36)	(San Miguel, Haematologica 2015; Lonial, Lancet 2016) Study STORM part 2
DOR	Duration from first response (at least PR) to time of progressive disease (PD) or death due to PD (per IRC), whichever occurred first.	Median, months	Selinexor 80 mg plus low-dose dexamethasone 20 mg (Sd) on Days 1 and 3 twice weekly	3.8	The duration of the responses shows a shorter duration in contrast to what is reported in the pomalidomide, daratumumab and belantamab mafodotin studies though in a population less pre-treated than that included in the STORM study. 95% CI (2.3,10.8)	(San Miguel, Haematologica 2015; Lonial, Lancet 2016; Lonial et al. Lancet Oncol. 2020)
OS (median, months)		(median, months)	Selinexor 80 mg plus low-dose dexamethasone 20 mg (Sd) on Days 1 and 3 twice weekly	8.4	Non interpretable data due to the design of the trial, i.e. single arm. 95% CI (5.9, 11.2)	
Unfavourable Effects						
AEs	Adverse events regardless causality		100%			
AEs grade ≥3	Adverse events grade 3-4 regardless causality		99%			
SAEs	Serious AEs regardless causality		60.7%			
Deaths*	Number of deaths related to Grade 5 AEs regardless causality		9.9%			
Thrombocytopenia	AE most commonly reported		75.2%			
Fatigue	AE most commonly reported		66.4%			
Anaemia	AE most commonly reported		60.3%			
Decreased appetite	AE most commonly reported		56.1%			

Effect	Short Description	Unit	Treatment	Result	Uncertainties/ Strength of evidence	References
Weight decreased	AE most commonly reported		49.1%			
Diarrhoea	AE most commonly reported		47.2%			
Vomiting	AE most commonly reported		42.5%			
Hyponatraemia	AE most commonly reported		39.7%			
Neutropenia	AE most commonly reported		36.4%			

Abbreviations: AE: Adverse event, CI: confidence interval, CR: complete response, DOR: duration of response, IRC: independent review committee, NR: not reached, ORR: overall response rate, PD: progression of disease, PO: oral administration, PR: partial response

*Notes: Safety data included in this table are taken from the 214 patients treated with selinexor 80 mg + dexamethasone twice weekly (202 patients from the phase 2 study KPT-330-012 and 12 patients from the phase 1 study KPT-330-001) [Cut-off date: 7 Sep 2019].*Deaths included in this table are only from study KPT-330-012.*

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

ORR decreases with each subsequent therapy in relapsed/refractory patients and complete responses are rarely achieved. With this in mind and even if some of the observed responses to treatment were challenged during previous assessment rounds within this procedure, the reported ORR of 25.3% (95% CI: 16.3, 36) in the penta-refractory group of patients (n=83) from the STORM study can be considered as clinically relevant in the intended treatment setting and expected to translate into clinically meaningful benefit in the proposed target population. The duration of the responses normally decreases after each line of therapy, as the disease becomes increasingly refractory. In the targeted patient population of penta-refractory patients, the reported median DOR was 3.8 months (95% CI: 2.3, 10.8) which can also be considered of certain relevance in the targeted highly pre-treated patient population.

The observed toxicity in the STORM study was clinically significant, including frequent severe haematological toxicity, especially thrombocytopenia and anaemia, and frequent severe nausea and vomiting, and fatigue. Further, a high number of patients required dose reductions and/or dose interruptions and more importantly, treatment discontinuation. However, even if the toxicity of selinexor is not negligible, it can be considered generally manageable with adequate monitoring and dose adjustment or discontinuation. The fact that the safety profile in the penta-refractory population was consistent with the safety for the whole population in Part 2 (n=123) concerning all AEs, SAEs and discontinuations due to AEs, with no new safety signals having been observed, is reassuring, since these patients are the most heavily pre-treated patients in the whole population included in the STORM study.

3.7.2. Balance of benefits and risks

The reported ORR of 25.3% (95% CI: 16.3, 36) in the penta-refractory group of patients (n=83) from the

STORM study can be considered as relevant in the intended treatment setting and expected to translate into clinically meaningful benefit in the proposed target population. The reported median DOR of 3.8 months (95% CI: 2.3, 10.8) can also be considered of certain relevance in the targeted highly pre-treated patient population.

Although the toxicity of selinexor is not negligible it is in line with what is expected in a setting where patients are heavily pre-treated and can be considered generally manageable with adequate monitoring and dose adjustment or discontinuation. Optimal risk minimisation measures in terms of dose modifications and supportive care are of course expected to be implemented, as well as monitoring of toxicity in the real-life setting.

Bearing all the above in mind, it is considered that available efficacy and safety data from the STORM study (n=83) support a favourable benefit/risk balance for the use of selinexor in combination with dexamethasone for the treatment of patients with multiple myeloma whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody. Limitations of the reported results coming from a single arm trial need to be addressed in the context of a conditional marketing authorisation and comprehensive data to address these remaining uncertainties will need to be provided by means of the specific obligation proposed.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease and is designated as an orphan medicinal product.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed above.
- It is likely that the applicant will be able to provide comprehensive data. The Applicant designed a confirmatory, Phase 3 (BOSTON), randomised, active comparator-controlled, open-label, multicentre (sites worldwide) study to compare the efficacy and assess the safety of selinexor plus bortezomib plus low-dose dexamethasone (SVd) versus bortezomib plus low dose dexamethasone (Vd) in ~364 adult patients with RRMM who have received 1 to 3 prior anti-MM regimens. After PD is confirmed by an Independent Review Committee (IRC), patients in the Vd arm may cross over to SVd treatment. Progression-free survival is the primary endpoint. This study has been designed as a confirmatory study to demonstrate and confirm the clinical benefit observed in STORM. It is therefore expected that the results of the BOSTON study (cut-off date February 2021) will suffice to address the remaining uncertainties and allow the switch from CMA to full approval for Sd in the applied indication.
- Unmet medical needs will be addressed, as RRMM is a condition where there are a number of

authorised treatment options but no curative treatments. Recently approved products for RRMM include lenalidomide, pomalidomide, bortezomib, carfilzomib, ixazomib, panobinostat, daratumumab, isatuximab, elotuzumab and belantamab mafodotin.

For 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 treatment options become very limited.

Additional treatment options are needed in RRMM aiming to achieve control and remission of the disease for as long as possible given that almost all patients eventually relapse and become resistant to available treatments, where the remission duration generally decreases with each subsequent treatment regimen, and where the toxicity of different regimens is significant and quite different between products. In this context, medicinal products with a positive benefit-risk balance and new mechanism of action can provide a major therapeutic advantage to patients if they offer possible alternative or additional treatment options based on a different safety profile, or based on therapeutic efficacy when other products are not expected to be effective.

On the basis of the data available for penta-refractory patients in the STORM study (n=83), ORR of 25.3% and median DOR of 3.8 months it can be concluded that selinexor in combination with dexamethasone has a positive benefit/risk balance in the revised, more restricted, penta-refractory MM patient population that addresses an unmet medical need in such heavily pre-treated patients. In the claimed indication, given the high unmet need, the observed ORR is expected to be associated with a clinical benefit in patients who respond and although low, the activity is considered sufficient to be of benefit. The benefits to public health of the immediate availability outweighs the risks inherent in the fact that additional data are still required.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. In view of the limited treatments options for the highly pre-treated patients whose disease is refractory to three classes of agents and the new mechanism of action, the immediate availability of Nexpovio on the market outweighs the risk inherent in the fact that additional data are still required.

3.8. Conclusions

The overall B/R of Nexpovio is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Nexpovio is not similar to Imnovid, Farydak, Ninlaro, Darzalex, Kyprolis and Blenrep within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Nexpovio is favourable in the following indication:

NEXPOVIO is indicated 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.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
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 results of the phase 3, KCP-330-023/BOSTON study (data cut off February 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.	May 2021

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that selinexor is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.