EU RISK MANAGEMENT PLAN FOR NEXPOVIO (SELINEXOR)

RMP version to be assessed as part of this application:

RMP Version number: 4.0

Data lock point for this RMP: 25 March 2025

Date of final sign off: 05 August 2025

Rationale for submitting an updated RMP:

Updates of the RMP are based on the study results from KCP-330-027

Summary of significant changes in this RMP:

- Removal of “use in severe hepatic impairment” from list of missing information included within the RMP based on the study results from KCP-330-027.

Other RMP versions under evaluation: None

RMP Version number: Not applicable

Submitted on: Not applicable.

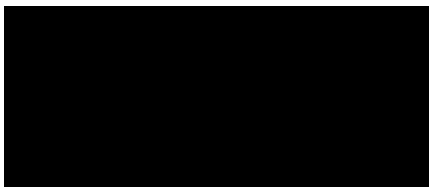
Details of the currently approved RMP:

Version number: 3.0

Date of positive CHMP opinion: 03 July 2023

Procedure number: EMEA/H/C/005127/IB/0014

QPPV name: Nawal Mahfoudh Jebbar

QPPV signature: 

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LIST OF ABBREVIATIONS

Acronym	Definition
AE	Adverse event
AKI	Acute kidney injury
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
BMI	Body mass index
BSA	Body surface area
CO_2	Carbon dioxide
CK	Creatine kinase
CL	Clearance
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CRM1	Chromosomal maintenance region 1 gene/protein (XPO1)
CSR	Clinical Study Report
CST	Company-Sponsored Trial
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DSUR	Development Safety Update Report
DLBCL	Diffuse Large B Cell Lymphoma
EEA	European Economic Area
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GBD	Global Burden of Diseases, Injuries, and Risk Factors
GLP	Good Laboratory Practices
hERG	Human ether-à-go-go-related gene
HM-Pool	Patients included in clinical trials on hematological malignancies (KCP-330-001, KCP-330-008, KCP-330- 009, KCP-330-010, KCP-330-012, KCP-330-013)
IC_{50}	50 % inhibitory concentration
IL	Interleukin
IL-6	Interleukin-6
IMiD	Immunomodulatory agent
INN	International Nonproprietary Names
IST	Investigator Sponsored Trial
IV	Intravenous
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple myeloma
MM-Pool	Patients in clinical trials on MM (KCP-330-001, KCP-330- 012, KCP-330-017, KCP-330-023)
MAO-B	Monoamine oxidase B
mRNA	Messenger ribonucleic acid
NES	Nuclear export sequence

NF-kB	Nuclear factor kappa B
NOAEL	No observed adverse effect level
NOEL	No observed effect level
OS	Overall survival
PI	Proteasome inhibitor
PIL	Patient Information Leaflet
PK	Pharmacokinetic(s)
PO	*per os* (by mouth, oral)
PT	Preferred Term
QT Interval	The interval between Q and T waves of the electrocardiogram
QT_c interval	Corrected QT interval
RBC	Red blood cell
RNA	Ribonucleic acid
RR	Relapsed/refractory
RRMM	Relapsed refractory multiple myeloma
SAE	Serious adverse event
SAR	Serious adverse reaction
SD	Sprague Dawley (rat)
SINE	Selective inhibitor of nuclear export
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA query
SOC	System Organ Class
STD	Standard deviation
T	Time
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
TLS	Tumor lysis syndrome
TNF	Tumor necrosis factor
TRAE	Treatment related adverse event
TRSAE	Treatment related serious adverse event
TSP	Tumor suppressor proteins
ULN	Upper limits of normal
WBC	White blood cells
XPO1	Exportin 1 (CRM1)

PART I. PRODUCT(S) OVERVIEW

Table Part I - 1: Product Overview

Active substance(s) (INN or common name)	Selinexor
Pharmacotherapeutic group(s) (ATC Code)	Selective Inhibitors of Nuclear Export (L01XX66)
Marketing Authorisation Holder (or Applicant)	Stemline Therapeutics B.V. Basisweg 10 1043 AP Amsterdam Netherlands
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	NEXPOVIO
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class; Selective Inhibitors of Nuclear Export
	Summary of mode of action: Selinexor (also known as KPT-330) is an oral, first-in-class, potent, slowly reversible ($t_{1/2}$~24 hours) covalent-binding Selective Inhibitor of Nuclear Export (SINE) compound that specifically blocks XPO1, also called chromosome region maintenance 1 (CRM1). XPO1 is overexpressed 2-4-fold in all cancers studied to date (including multiple myeloma (MM)) and high levels of expression are frequently correlated with poor prognosis and / or reduced survival. XPO1 is the exclusive nuclear transporter for shuttling the major tumor suppressor proteins (TSPs) and other growth regulators out of the nucleus. Since TSPs require nuclear localization to mediate their tumor suppressing functions, nuclear export leads to their functional inactivation. In addition, XPO1 mediates the nuclear-to-cytoplasmic transport of the mRNAs for several oncoproteins (associated with the XPO1- binding carrier molecule eIF4E) including c-Myc, Cyclin D, BTK, Flt3 and Bcl2 family proteins leading to increased cytoplasmic ribosomal translation and higher levels of these mitogenic and pro-survival proteins. Blockade of XPO1 leads to marked accumulation of TSPs in the nucleus of all cells, leading to cell cycle arrest at the G1±G2 checkpoints, inhibition of DNA damage repair and of the NF-κB pathway. Cancer cells undergo apoptosis, whereas normal cells remain in cell cycle arrest until the XPO1 block is released and they resume normal activities. Blocking of XPO1 similarly leads to decrease in the nuclear-to-cytoplasmic transport of mRNAs for several oncoproteins (see above) with consequent reductions in their protein levels.

	Consistent with its activation of multiple TSPs and reductions in several oncoproteins, selinexor has shown broad anti-cancer activity in murine models. Similarly, evidence of broad anti- tumor activity in patients with hematologic (including MM) and solid tumor malignancies, many of whom have received all available standard anti-cancer agents, suggest that XPO1 inhibition is a mechanism relevant to the treatment of diverse human cancers.
	Important information about its composition: Selinexor 20 mg tablets contain 12.5 % by weight of the active pharmaceutical ingredient as well as microcrystalline cellulose; croscarmellose sodium (disintegrant]; Kollidon 30 powder (solubilizing agent); colloidal silicon dioxide (anti-caking agent); magnesium stearate (lubricant). Additional inactive excipients include microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, sodium lauryl sulphate, and magnesium stearate.
Hyperlink to the Product Information	*Include a link or reference to the proposed PI in the eCTD sequence.*
Indication(s) in the EEA	Current: NEXPOVIO is indicated: - in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy - 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
	Proposed; Not applicable
Dosage in the EEA	Current: The recommended selinexor, bortezomib and dexamethasone doses for administration of selinexor with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy are as follows: • Selinexor 100 mg taken orally once weekly on Day 1 of each week. • Dexamethasone 20 mg taken orally twice weekly on Days 1 and 2 of each week. • Bortezomib 1.3 mg/m^2 administered subcutaneously once weekly on Day 1 of weeks 1-4 with week 5 off. The recommended selinexor and dexamethasone starting doses for administration of selinexor 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 are as follows:

	• Selinexor 80 mg taken orally once weekly on Days 1 and 3 of each week. • Dexamethasone 20 mg taken orally on Days 1 and 3 of each week with selinexor.
	Proposed; Not Applicable
Pharmaceutical form(s) and strengths	Current: Selinexor (KPT-330) is formulated as 20 mg tablets for oral administration. Selinexor 20 mg tablet is a blue, round, bi-convex, film-coated tablet with “K20” debossed on one side.
	Proposed; Not Applicable
Is / will the product be subject to additional monitoring in the EU?	Yes

PART II. SAFETY SPECIFICATION

PART II: MODULE SI. EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION INDICATION

NEXPOVIO is indicated:

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

Incidence
The incidence of MM in Europe is 4.5–6.0 new cases per 100,000 people per year with a median age at diagnosis of 72 years; the mortality is 4.1/100,000/year (*Moreau et al., 2017*).

In 2015, there were 40,000 new cases and an estimated 21,500 deaths from MM in Europe (*Schey et al., 2016*, *Myeloma Patients Europe, 2017*). Furthermore, the number of new cases of MM in Europe is expected to increase to almost 46,000 by 2025 (*Myeloma Patients Europe, 2017*) and the number of deaths attributed to MM in Europe is estimated to increase to over 27,000 by 2030 *(Schey et al., 2016*).

In the United States in 2018, there will be an estimated 30,770 new cases and 12,770 deaths. These numbers are age adjusted and based on assumptions made using data from 2015 (*SEER, 2018).*

Prevalence
Multiple myeloma is the second most prevalent blood cancer (10 %) worldwide, after non-Hodgkin's lymphoma. Globally, multiple myeloma affected about 358,000 people with a corresponding estimated 70,000 years living with disability (*GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017*). The disease resulted in 98,400 deaths in 2016, 1.5 per 100,000 people per year (*GBD 2016 Causes of Death Collaborators, 2017*).

The prevalence of MM was estimated at about 14,000 patients each in France and the UK, about 19,000 in Germany and about 13,000 patients in Italy (*Cure Research, 2003*).

The prevalence in the US was estimated at 124,733 people for 2015 and the mortality as 3.3 per 100,000 people per year. Multiple myeloma represents approximately 1.8 % of all new cancers and 2.1 % of all cancer deaths (*SEER, 2018*).

Multiple myeloma is largely a disease of older adults, with a median age at diagnosis of > 65 years. A consistent and continuous increase in life expectancy is recorded worldwide and the global population is rapidly aging. Consequently, the number of patients with MM is expected to increase considerably by nearly 80 % each year in the next 2 decades (*Larocca & Palumbo, 2015*).

Demographics of the population in the proposed indication – age, gender, racial and / or ethnic origin and risk factors for the disease

The median age at diagnosis of MM is 65-70 years; only 2 % of patients are younger than 40 years (*Raab et al., 2009*). The incidence of MM increases with age.

Multiple myeloma affects slightly more men than women. For example, in the UK, 58 % of MM cases are in males, and 42 % are in females (*Cancer Research UK, 2018*).

Regarding race and ethnicity, African Americans have the highest reported incidence of this disease and Asians the lowest. Results of a recent study found the incidence of myeloma to be 15.9 and 11.6 cases per 100,000 for male and female African Americans, respectively, and 7.9 and 4.7 cases, respectively, per 100,000 Caucasian Americans (*SEER, 2018*).

Farming, occupation as a firefighter or hairdresser, exposures to chemicals or pesticides, patterns of alcohol intake, pernicious anaemia and ankylosing spondylitis may be associated with an increased risk of developing MM. Inherited risk factors are thought to be explained by gene polymorphisms and acquired risk factors are thought to be associated with gene promoter methylation (*Sergentanis et al., 2015*).

Precursor Pathologies

The majority, if not all, cases of MM are believed to be preceded by a condition known as Monoclonal Gammopathy of Undetermined Significance or MGUS (*Landgren et al., 2009*). MGUS includes the presence of abnormally elevated levels of a monoclonal protein but without clinical signs or symptoms of frank MM. MGUS transforms to MM at the rate of 1 % to 2 % per year, and almost all cases of multiple myeloma are preceded by MGUS. A more advanced entity, designated smouldering MM, is associated with higher levels of monoclonal protein and malignant bone marrow plasma cells than MGUS, also lacks signs and symptoms of overt MM, and carries an increased risk of developing frank MM. Individuals diagnosed with this premalignant disorder develop frank MM at a rate of 10 % per year for the first 5 years, 3 % per year for the next 5 years, and then 1 % per year (*Dutta et al., 2017*).

Common Symptoms and Signs of MM

MM is typically characterized by the “CRAB” sign criteria: hypercalcaemia, renal dysfunction, anaemia and bone disease. Further complications of MM can occur as side effects of treatment or as the result of advanced disease. Typical co-morbidities with multiple myeloma are anaemia and resulting fatigue (often highly significant), renal dysfunction, hypogammaglobulinemia associated increased risk for infection, increased risk of cardiovascular disease, pathologic fractures due to osteopenia and lytic bone lesions, high serum protein (raised monoclonal immunoglobulin level) which can increase serum viscosity. Side effects limiting the optimal use of treatment regimens are mostly gastrointestinal, cardiac, neurological, renal and infection- related toxicities.

Main Existing Treatments

The treatment of MM was originally restricted to glucocorticoids, alkylating agents and other chemotherapeutics, and outcomes were almost universally poor. Treatment has improved over the last 20 years and overall survival (OS) has increased considerably with the advent of high dose alkylating (ablating) chemotherapy with rescue by autologous stem cell transplantation and more importantly, with the approval of non-chemotherapy agents including IMiDs such as thalidomide, lenalidomide, and pomalidomide, and the proteasome inhibitors (PIs) bortezomib and carfilzomib and more recently oral ixazomib along with the anti-CD38 monoclonal antibody (mAb) daratumumab. These agents (other than ixazomib) are typically

used in combination with "low- dose" dexamethasone (i.e., ≤ 40 mg/week) and often in combination with other classes of drugs.

Additional drug classes, including histone deacetylase inhibitors such as panobinostat and anti- CS1 mAb elotuzumab, as well as ixazomib, have been approved *only in combination* with either IMiDs or PIs; these may provide additional benefit in MM in patients whose disease is not refractory to IMiDs or PIs.

The major treatment regimens including dosing schedules for patients with RRMM according to current ESMO guidelines *(Moreau et al., 2017*) are listed below.

- Carfilzomib/lenalidomide/dexamethasone (KRd):
  Carfilzomib 20 mg/m^2 (cycle 1) and 27 mg/m^2 (subsequent cycles) i.v. on days 1, 2, 8, 9, 15, 16; lenalidomide 25 mg orally days 1–21; dexamethasone 40mg on days 1, 8, 15, 22; 28-day cycles
- Bortezomib/dexamethasone/panobinostat (VD-Pano):
  Bortezomib 1.3 mg/m^2 subcutaneously days 1, 8, 15, 22; dexamethasone 20mg on day of and day after bortezomib; panobinostat 20 mg orally days 1, 3, 5 week 1 and 2; repeated every 3 weeks (cycles 1–8)
- Carfilzomib/dexamethasone (Kd):
  Carfilzomib 56 mg/m^2 i.v. days 1, 2, 8, 9, 15, 16 (20 mg/m^2 days 1, 2, cycle 1 only); dexamethasone 20mg days 1, 2, 8, 9, 15, 16, 22, 23; 28-day cycles
- Lenalidomide/dexamethasone/elotuzumab (Rd-Elo):
  Lenalidomide 25mg orally days 1–21; dexamethasone 40mg weekly; elotuzumab 10 mg/kg i.v. weekly cycle 1 and 2, every other week cycles 3þ; repeated every 28 days.
- Lenalidomide/dexamethasone/ixazomib (IRd):
  Lenalidomide 25mg orally days 1–21; dexamethasone orally 40mg days 1, 8, 15, 22; ixazomib 4mg orally days 1, 8, 15; repeated every 28 days.
- Bortezomib/dexamethasone/daratumumab (DVd):
  Bortezomib 1.3 mg/m^2 subcutaneously days 1, 4, 8, 11 (cycles 1–8); dexamethasone 20mg orally days 1, 2, 4, 5, 8, 9, 11, 12 (cycles 1–8); daratumumab 16 mg/kg i.v. every week (cycles 1–3), every 3 weeks (cycles 4–8), every 4 weeks (cycles 9þ); cycles 1–8: repeated every 21 days; cycles 9+: repeated every 28 days.
- Lenalidomide/dexamethasone/daratumumab (DRd):
  Lenalidomide 25mg orally days 1–21; dexamethasone 40mg orally weekly; daratumumab 16 mg/kg i.v. weekly (cycles 1-2), every other week (cycles 3-6), every 4 weeks (cycles 7+).

For patients with triple class refractory (refractory to an IMiD, PI and an anti-CD38 mAb) MM, there is currently only one treatment in this indication under conditional marketing authorization with demonstrated clinical benefit. Therefore, there remains a high unmet medical need for new therapies for patients, particularly those with novel mechanisms that can prevent disease progression and improve the OS of patients with MM whose disease is refractory to the available approved agents.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

The survival rates and disease progression for RRMM depend on many factors, including characteristics of the disease and defined prognostic factors, access to novel therapies, and patient specific factors including age, co morbidities, and fit vs frail.

According to current German data (*DGHO, 2018*), 5-year survival rates are estimated at 41 % for males and 40 % for females. When general mortality rates are considered the relative 5-year survival rates are estimated at 48 % for males and 45 % for females. Relative 10-year survival rates are estimated at 31 % for males and 30 % for females.

MM in Older Persons

Although effective novel agents and supportive care have substantially improved outcomes across all age groups, patients with MM > 75 years old have a shorter survival. Older patients with MM may be in poorer general health, and therefore considered ineligible for stem cell transplants. Similarly, they may be unable to tolerate strong or sustained chemotherapy. Aging is a complex process characterised by a gradual, progressive decrease in physiological reserve, with changes in body composition and clinically significant reductions in renal, gastric, hepatic, and cardiovascular functions. It is commonly associated with the concomitant occurrence of multiple diseases (comorbidities), need for polypharmacy to treat these conditions and an increased risk of developing physical and cognitive decline (disability). Older persons also have an increased risk of becoming frail, and this is common in MM with approximately one-third of patients MM at diagnosis considered frail (*Larocca & Palumbo, 2015*). Frailty is a state of increased vulnerability, with cumulative deficits in several physiological systems, which results in diminished resistance to stressors such as multiple myeloma and its treatment. This state has a negative effect on patients' quality of life (QoL) and on treatment efficacy and tolerability, with a consequent increase in health care costs. Considering the elderly population, the choice of therapy should focus not only on the quality of response but also on maintaining an independence status and preserving cognitive function and QoL (*Larocca & Palumbo, 2015*).

PART II: MODULE SII. NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key Safety findings (from non- clinical studies)	Relevance to human usage
Toxicity	
Genotoxicity testing using Ames test, *in vivo* micronucleus assay in SD rats and *in vitro* chromosome aberration test in cultured human peripheral blood lymphocytes did not suggest a genotoxic potential of selinexor.	No concerns raised.
A neutral red uptake assay conducted using 3T3 fibroblasts suggested that selinexor is not phototoxic.	No concerns raised.
Single and repeat-dose toxicology studies in SD rats and cynomolgus monkeys were conducted. The primary adverse toxic effects of selinexor in rats and monkeys are reduced food intake and associated weight loss, decreased body weight gain, along with histological changes in male and female reproductive and immune system organs. Mortality was observed in rats and monkeys and was attributed to primarily profound inhibition of weight gain, mild to moderate gastrointestinal changes, bone marrow effects (hypocellularity, necrosis), and lymphoid depletion. In rats and	Decreased body weight over time, effects on gastrointestinal system, bone marrow, and lymphoid organs with some central nervous system toxicity. Types of infections observed in clinical studies were consistent with patients with advanced heavily pretreated malignancies; opportunistic or atypical infections were not typically associated with selinexor treatment. Specific cerebellar

monkeys, mortality was preceded by rapid weight loss and in surviving animals there was recovery of the effects on body weight. Some central nervous system toxicity, i.e., necrosis of cerebellar granular cells, was noted in monkeys in 2- week studies at doses which yielded exposures > 2 times. the exposure in humans receiving selinexor at the recommended starting dose of 80 mg.	toxicity was not observed in patients with hematologic malignancies at the dose (80 mg) proposed here.
In an oral (gavage) study in rats, no adverse maternal effects were noted at 0.25 mg/kg/day, but lower mean body weight gains and corresponding lower mean food consumption were observed at 0.75 and 2 mg/kg/day. Developmental effects (lower foetal weights) were noted at 0.75 and 2 mg/kg/day. Foetal skeletal developmental variations were noted in the 0.75 and 2 mg/kg/day groups. These findings indicate developmental delay and correlated with lower foetal weights. A selinexor dosage level of 0.25 mg/kg/day (1.5 mg/ m^2) was considered to be the no observed adverse effect level (NOAEL) for maternal toxicityand embryo / foetal development. There are no data on lactating animals (a pre / postnatal study was not conducted), and levels of selinexor in milk are not known. Toxicity of the male reproductive system was observed in rats and monkeys, i.e., atrophy / necrosis of testes. Toxicity of the female reproductive system was observed in a 4-week rat study, including lower ovary / oviduct and uterus / cervix weights associated with decreased ovarian follicles and uterine atrophy. In addition, interstitial cell hyperplasia was observed in the ovary, as well as vaginal and cervical mucification / stratified squamous hyperplasia.	Based on selinexor's mechanism of action and findings from animal studies, it may cause foetal harm in animals and should not be administered in patients who are pregnant or nursing as there are no data in these populations. In addition, selinexor may impair fertility in males and females.
In a guinea pig skin sensitization – maximisation test, intradermal induction with 5 % selinexor in mineral oil and a topical induction with 25 % selinexor in mineral oil followed by topical challenge with 25 % selinexorto guinea pigs elicited a mild grade II dermal contact hypersensitivity response at 24 and 48 hours.	No concerns raised for the proposed oral administration.

Safety pharmacology	
Selectivity: A large panel of in vitro protein binding assays was performed to evaluate the potential interaction of selinexor at various principal receptor / ligand interactions, (peptides, growth factors, ion channels; N = 43) kinases (N = 54), and cysteine proteases (including caspases and matrix metalloproteinases; N = 17). Selinexor did not significantly (< 50 % inhibition) bind to any of the receptors studied, with the exception of Monoamine Oxidase B (MAO-B). In a separate study, using a functional assay, there was no detectable inhibition of MAO-B by selinexor. Given these results, selinexor is considered to be a highly selective agent with limited potential for off target effects.	No concerns raised.
Cardiovascular effects: The potential for selinexor-mediated cardiac electrophysiologic changes was assessed in a GLP in vitro human ether-à-go-go related gene (hERG) channel current inhibition assay. No effect on any cardiac interval, including QTc, was detected in this study orin separate 1- or 3-month monkey toxicology studies.	No concerns raised.
Behavior, physiology, and neurological effects (Irwin Test): Selinexor was evaluated for its potential to induce gross behavioral, physiological, and neurological effects in a single-dose, GLP study in SD male rats. Oral (gavage) administration of selinexor to male SD rats at 2 or 10 mg/kg did not affect the gross behavioral, physiological, or neurological state of the animals. Lower body temperature (0.9 °C drop that was statistically significant) was noted following administration of 50 mg/kg selinexor. The transient	Drop of body temperature at high doses was not observed in clinical studies.

Key Safety findings (from non- clinical studies)	Relevance to human usage
effect on body temperature (full recovery by 24 hours) may be related to reductions in pyrogenic cytokines such as IL1, IL6, or TNFα which are known effects of XPO1 inhibition. Under the conditions of this study, the no-observed-effect level (NOEL) for selinexor was 10 mg/kg, PO. <u>Respiratory effects:</u> Selinexor was evaluated for acute respiratory effects in male SD rats. In this single-dose study, selinexor was administered via PO gavage at 2, 10, or 50 mg/kg. Selinexor had a statistically significant effect on reducing the minute volume ($\dot{V}$; total volume inhaled in 1 minute), with both respiratory frequency and tidal volumes reduced at doses of 10 and 50 mg/kg through 300 minutes post dose. The maximal reduction in $\dot{V}$was 30 % and 40 % compared to baseline $\dot{V}$ at 10 and 50 mg/kg. Since CO_2 production is the major driver for respiration in normoxic animals, it is likely that the reduction in $\dot{V}$ is associated with reduced CO_2 production, possibly from reduced food intake / metabolism. As noted above in the Irwin test, the behavior of the animals is not affected, but reduced CO_2 production from food metabolism is anticipated at these doses, which did cause anorexia in 2-, 4-, and 13-week toxicology studies. There were no significant changes at 2 mg/kg (12 mg/m^2) dose in any respiratory parameter, indicating that this is the NOEL in this study.	Drop of respiratory volume was not observed in clinical studies.
Pharmacokinetic interactions	
The very low turnover in human liver microsomes and recombinant enzymes suggested selinexor is metabolically stable and unabsorbed parent contributes to substantial disposition of selinexor. The limited metabolism was catalyzed by CYP3A4 (and not the other CYPs) and UGTs; however, sensitivity to these enzymes is low. Selinexor is not a substrate for major metabolic transporters BCRP, Pgp, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, and MATE2. Selinexor did not inhibit SLC transporters except for marginal inhibition of OATP1B1 and 1B3, which may not be clinically relevant. The potential for drug interactions due to inhibition of major human CYPs is very low (all concentration resulting in IC50 values > 10 μM), including CYP3A4/5 IC50 of 24 μM and no demonstrable CYP induction is observed.	No concerns raised as in vitro data are consistent with a lack of reported drug-drug interactions amongst the > 1100 patients with heavily pretreated MM who have received selinexor.

Other toxicity-related information or data	
Key Safety findings (from non- clinical studies)	**Relevance to human usage**
Selinexor had little effect on normal (non-malignant) haematopoietic stem and progenitor cells (*Etchin et al., 2016),* lymphocytes or other nontransformed cells. Selinexor reduces platelet counts without affecting platelet function, and with minimal effects on numbers of megakaryocytes. Selinexor's effects on platelet generation are primarily related to blocking an early step in the differentiation of hematopoietic stem cells to megakaryocytes (*Machlus et al 2017*). No carcinogenicity studies have been performed for selinexor.	In short-term toxicology studies, effects were observed in male and female reproductive organs in monkeys and developmental effects were seen with daily exposure in rats. Carcinogenicity studies have not been conducted with selinexor. Selinexor was not mutagenic in vitro in a bacterial reverse mutation (Ames) assay and was not clastogenic in either the in vitro cytogenetic assay in human lymphocytes or in the in vivo rat micronucleus assay. Fertility studies in animals have not been conducted with selinexor. In repeat-dose oral toxicity studies, selinexor was administered for up to 13 weeks in rats and monkeys. Reduced sperm, spermatids, and germ cells in epididymides and testes were observed in rats at ≥ 1 mg/kg, decreased ovarian follicles were observed in rats at ≥ 2 mg/kg, and single cell necrosis of testes was observed in monkeys at ≥ 1.5 mg/kg. These dose levels resulted in systemic exposures approximately 0.11, 0.28, and 0.53 times, respectively, the exposure (AUClast) in humans at the recommended human dose of 80 mg

PART II: MODULE SIII. CLINICAL TRIAL EXPOSURE

Cumulatively as of 25 March 2025, 6,261 patients with hematologic or solid tumors had received at least 1 dose of selinexor or blinded study drug in Karyopharm Sponsored Trials (CSTs) (selinexor in 2,699 patients, selinexor/placebo in 588 patients and selinexor/elotuzumab in 124 patients [collaborative study EMN29]), ISTs (2,269 patients from Karyopharm-managed ISTs, and 177 patients from Antengene-managed ISTs), Ono-sponsored study (9 patients), and Antengene-sponsored studies (395 patients). Antengene Therapeutics Ltd, a partner of Karyopharm, holds the MAH for selinexor in Taiwan, Hong Kong, Macau, South Korea, Singapore, and Australia, and also sponsors selinexor studies in China. Ono pharmaceutical Co. Ltd is responsible for selinexor clinical trials which are categorised as non-company sponsored trials.

Tabular summaries are provided below in *Table SIII - 1* to *Table SIII - 4* describing patient population / demographics and patient exposure in CSTs. The presented data reflects the information provided in selinexor PBRER v6.0.

Table SIII - 1: Summary of Estimated Number of Patients Exposed to Selinexor in Karyopharm Company-Sponsored Trials by Age and Gender

	Number of Patients (n = 3,411)		
Age (year)[1]	**Male**	**Female**	**Total**
< 18	0	0	0
18 to 50	226	187	413
51 to 64	570	611	1182 *
65 to 74	652	632	1284
≥ 75	286	246	532
Total	**1,734**	**1,676**	**3,411***

[1] Age is based on calculation of same at the date of first dose.
* There is 1 patient with missing gender information for 51-64 age group
Exposure data as of the DLP 25March2025

Table SIII - 2: Summary of Estimated Cumulative Number of Patients Exposed to Selinexor in Karyopharm Company-Sponsored Trials by Racial Group

Racial Group	Total Number of Patients
White	2854
Black or African American	171
Asian	149
Other	155
Unknown / Missing / Not provided / Not reported	65
Native Hawaiian or Other Pacific Islander	8
Multiple	6
American Indian or Alaska Native	3

Table SIII - 3: Estimates of Cumulative Number of Patients Exposed in Karyopharm Company-Sponsored Trials Based on Enrolment / Randomisation Schemes

Treatment	Number of Patients
Selinexor/Placebo[1]	588
Selinexor	2699
Selinexor/Elotuzumab	124

* This includes safety patients in 024, 042 and 034 Phase 3; * There is 1 patient with missing gender information for 51-64 age group

Table SIII - 4: Summary of Estimated Cumulative Number of Patients Exposed to Selinexor in Karyopharm Company-Sponsored Trials by Cancer Type

Cancer Type	n (N = 3411)
Multiple Myeloma (MM)	1,019
Diffuse large B-cell lymphoma (DLBCL)	376
Acute myeloid leukemia (AML)	308
Hematologic Excluding AML, DLBCL and MM	353
Solid Tumors	1355

Exposure data as of the DLP 25March2025

In the Ono-sponsored trial, 9 Asian patients were enrolled and dosed: 5 males and 4 females, all age 51 and above. Five patients with MM and 4 patients with other hematologic cancers.

Cumulatively, in Antengene-sponsored trials, 395 Asian patients were enrolled and dosed with selinexor (368 patients) or a comparator treatment (27 patients): 221 males and 174 females, all of age 18 and above. Of the 395 patients, selinexor was indicated for MM in 234 patients, for DLBCL in 105 patients, and for other hematological malignancies in 56 patients.

Table SIII - 5 and below data represents the pooled data analyses of clinical data with a cut-off date of 07 September 2019. The datasets included in this RMP for the time of registration remain current for the approved indication and no significant changes to the product's safety profile or risk management activities have been identified to warrant an update.

Table SIII - 5: Summary of Cumulative Exposure to Selinexor in Company-Sponsored Trials by Cancer Type as of 07 September 2019

	MM (N = 686)	AML (N = 308)	Hematological Excluding AML and MM (N = 418)	Solid Tumors (N = 664)	All Patients (N = 2076)
Cumulative Dose (mg)					
N	686	308	418	549	1961
Median	1060.0	720.0	720.0	800.0	840.0
Mean	1575.3	1092.5	1363.4	1293.1	1375.3
(STD)	(1546.39)	(1145.40)	(1875.35)	(1448.99)	(1550.80)
Min, Max	20, 13780	45, 8940	60, 13860	50, 11440	20, 13860

[a] Includes 115 patients from blinded, placebo-controlled study KCP-330-020 Pooled data cut-off date: 07 September 2019

The Pools include only the available data from studies in hematological malignancies (HM-Pool; *Table SIII - 6*) and studies in MM (MM-Pool). The MM- Pool also includes data from studies with enrollment still ongoing. The pooled data are based on the clinical data with a cut-off date of 07 September 2019. The Sponsor is not aware of any new clinically significant safety observations since the cut-off date of 07 September 2019.

In the HM-Pool, the median age of patients was 68.0 years (range 18 to 94). The majority of patients were male (59.1 %), and the most frequently reported race was White (82.1 %), followed by Black or African American (7.2 %), then other (4.9 %). In the MM-Pool, the median age of patients was 64.5 years (range 34, 86). The majority of patients were male (54.9 %), and the most frequently reported race was White (79.2), followed by Black or African American (10.5 %), then Asian (4.5 %).

The MM-Pool includes all patients with MM who were treated using various selinexor dose levels and treatment regimens investigated in Phase 1, Phase 2, and Phase 3 studies. The proposed selinexor dose for registration is 80 mg (equivalent to ~45 mg/m^2 body surface area [BSA]) plus dexamethasone 20 mg twice weekly. Exposure for those patients treated at the proposed selinexor dose with dexamethasone are presented in the column labelled ‘S(80 mg)dex’, those treated with other selinexor doses with or without dexamethasone are presented under ‘other S±dex’, and all treated patients with MM are presented under ‘All MM’; see *Table SIII - 7.*

Table SIII - 6: Summary of Cumulative Exposure to Selinexor in Company-Sponsored Hematological Malignancy Trials by Cumulative Dose (HM-Pool)[a]

	0-500 mg (N = 343)	501-1000 mg (N = 298)	1001-2000 mg (N = 212)	2001-3000 mg (N = 63)	3001-5000 mg (N = 53)	> 5000 mg (N = 27)	Total (N = 996)
Duration of Exposure (weeks)							
n	343	298	212	63	53	27	996
Median	3.0	6.0	13.0	21.0	36.0	75.0	6.0
Mean (STD)	3.1 (1.90)	7.3 (9.34)	14.9 (10.05)	23.2 (9.42)	39.7 (15.22)	78.7 (28.46)	12. 1 (17.12)
Min, Max	1, 21	2, 161	4, 113	9, 62	15, 92	36, 134	1, 161
Duration of Exposure n (%)							
< 4 Weeks	234 (68.2)	17 (5.7)	0	0	0	0	251 (25.2)
4-< 12 Weeks	107 (31.2)	262 (87.9)	80 (37.7)	2 (3.2)	0	0	451 (45.3)
12-< 24 Weeks	2 (0.6)	18 (6.0)	109 (51.4)	37 (58.7)	3 (5.7)	0	169 (17.0)
24-< 48 Weeks	0	0	20 (9.4)	23 (36.5)	36 (67.9)	2 (7.4)	81 (8.1)
≥ 48 Weeks	0	1 (0.3)	3 (1.4)	1 (1.6)	14 (26.4)	25 (92.6)	44 (4.4)
Missing	0	0	0	0	0	0	0
Number of Doses Received							
n	343	298	212	63	53	27	996
Median	5.0	10.0	20.0	33.0	56.0	104.0	10.0
Mean (STD)	5.2 (2.84)	10.7 (3.85)	21.0 (7.49)	35 (12.47)	59.4(23.04)	121.9 (48.51)	18.1 (24.39)
Min, Max	1, 28	4, 39	6, 59	18, 95	29, 135	59, 237	1, 237
Total Dose Received (mg)							
n	343	298	212	63	53	27	996
Median	360.0	700.0	1360.0	2460.0	3580.0	7210.0	720.0
Mean (STD)	319.3 (131.61)	720.1 (138.89)	1407.5 (278.71)	2471.9 (305.15)	3798.8 (589.93)	7715.3 (2415.18)	1192.7 (1471.10)
Min, Max	40, 500	510, 1000	1020, 2000	2015, 3000	3040, 4925	5035, 13780	40, 13780
Average Dose Received n (%)[b]							
0 - 40 mg/dose	30 (8.7)	8 (2.7)	7 (3.3)	1 (1.6)	2 (3.8)	1 (3.7)	49 (4.9)
41 - 60 mg/dose	163 (47.5)	126 (42.3)	83 (39.2)	16 (25.4)	21 (39.6)	10 (37.0)	419 (42.1)
61 - 80 mg/dose	94 (27.4)	87 (29.2)	62 (29.2)	21 (33.3)	18 (34.0)	14 (51.9)	296 (29.7)
81 - 100 mg/dose	43 (12.5)	65 (21.8)	43 (20.3	19 (30.2)	8 (15.1)	1 (3.7)	179 (18.0)
> 100 mg/dose	13 (3.8)	12 (4.0)	17 (8.0)	6 (9.5)	4 (7.5)	1 (3.7)	53 (5.3)
Dose Intensity (mg/week)[a]							
n	343	298	212	63	53	27	996
Median	120.0	112.5	109.2	115.0	106.3	104.5	113.3

	0-500 mg (N = 343)	501-1000 mg (N = 298)	1001-2000 mg (N = 212)	2001-3000 mg (N = 63)	3001-5000 mg (N = 53)	> 5000 mg (N = 27)	Total (N = 996)
Mean (STD)	117.6 (44.15	119.1 (41.80)	113.9 (43.24)	120.9 (42.34)	104.4(35.33)	102.3 (21.93)	116.4 (42.34)
Min, Max	10 , 240	4 , 270	12 , 260	37 , 238	51 , 213	62 , 156	4 , 270

[a] All CSTs (enrolment completed) of selinexor in hematological malignancies with data available (KCP-330-001, KCP-330-008, KCP-330-009, KCP-330-010, KCP-330-012, KCP-330-013); data cut-off date: 07 September 2019.

[b] Average dose received = total dose received / number of doses received.

[c] Dose intensity = total dose received / duration of exposure.

Table SIII - 7: Summary of Cumulative Exposure to Selinexor in Company-Sponsored Trials in Multiple Myeloma Patients by Cumulative Dose (MM-Pool)[a]

	All MM[b] (N = 552)	S(80 mg)+dex (N = 214)	Other S+dex (N = 71)
Duration of Exposure (weeks)			
n	552	214	71
Median	9.0	8.5	5.0
Mean (STD)	15.8 (18.88)	12.3 (11.88)	10.6 (16.86)
Min, Max	1, 140	1, 76	1, 106
Duration of Exposure n (%)			
< 4 Weeks	101 (18.3)	47 (22.0)	21 (29.6)
4-< 12 Weeks	208 (37.7)	85 (39.7)	35 (49.3)
12-< 24 Weeks	138 (25.0)	51 (23.8)	9 (12.7)
24-< 48 Weeks	71 (12.9)	26 (12.1)	2 (2.8)
≥ 48 Weeks	34 (6.2)	5 (2.3)	4 (5.6)
Missing	0	0	0
Number of Doses Received			
n	552	214	71
Median	11.0	11.0	9.0
Mean (STD)	18.4 (22.67)	17.5 (17.92)	19.2 (34.16)
Min, Max	1, 228	1, 135	1, 228
Total Dose Received (mg)			
n	552	214	71
	All MM[b] (N = 552)	**S(80 mg)+dex (N = 214)**	**Other S+dex (N = 71)**
Median	880.0	830.0	500.0
Mean (STD)	1322.7 (1429.02)	1251.0 (1117.39)	1064.9 (1853.17)
Min, Max	40, 13780	80, 6220	40, 13780

Average Dose Received n (%)[c]			
0 - 40 mg/dose	20 (3.6)	1 (0.5)	15 (21.1)
41 - 60 mg/dose	82 (14.9)	18 (8.4)	23 (32.4)
61 - 80 mg/dose	236 (42.8)	170 (79.4)	12 (16.9)
81 - 100 mg/dose	202 (36.6)	23 (10.7)	12 (16.9)
> 100 mg/dose	12 (2.2)	2 (0.9)	9 (12.7)
Dose Intensity (mg/week)[d]			
n	552	214	71
Median	97.9	112.4	103.0
Mean (STD)	98.6 (35.84)	116.4 (34.80)	107.9 (48.27)
Min, Max	7, 248	22, 240	10, 248
Assigned Dosing Frequency n (%)			
Once Weekly	234 (42.4)	0	2 (2.8)
Twice Weekly	293 (53.1)	214 (100.0)	44 (62.0)
Other	25 (4.5)	0	25 (35.2)

[a] All CSTs of selinexor in MM with data available (KCP-330-001, KCP-330-012, KCP-330-017, KCP-330-023); data cut-off date: 07 September 2019.

[b] The numbers in the All MM group include patients treated with selinexor in combination with other antimyeloma agents; therefore, the totals in the All MM group are greater than the sum of the S(80 mg)+dex and Other S+dex groups

[c] Average dose received = total dose received / number of doses received.

[d] Dose intensity = total dose received / duration of exposure.

PART II: MODULE SIV. POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Pregnant women, women actively trying to become pregnant.

Reason for exclusion: Selinexor can potentially cause fetal harm when administered to a pregnant woman based on findings in animals.

Is it considered to be included as missing information? No

Rationale: There are no known or expected safety concerns for use in the target population.

Nursing women

Reason for exclusion: No data are available regarding the presence of selinexor or its metabolites in human milk, or on its effects on the breastfed infant or milk production. Because of the potential for serious adverse reactions in breastfed infants from selinexor, lactating women should not breastfeed during treatment with selinexor.

Is it considered to be included as missing information? No

Rationale: There are no known or expected safety concerns for use in the target population.

Non-adequate hepatic function

Reason for exclusion:

The clinical development program for selinexor initially focused on patients with adequate hepatic function, defined as total bilirubin < 2x upper limit of normal (ULN) (or < 3x ULN for Gilbert's syndrome), aspartate aminotransferase (AST) < 2.5x ULN, and alanine aminotransferase (ALT) < 2.5x ULN within three weeks prior to the first dose. This approach aimed to minimize confounding factors in data analysis regarding safety.

However, subsequent studies have provided further insights into selinexor's safety profile in patients with hepatic impairment. In the HM-Pool, which included 996 patients, there were 137 patients with mild hepatic impairment (total bilirubin > 1.5x ULN or AST > ULN), 11 patients with moderate hepatic impairment (total bilirubin > 1.5-3x ULN any AST), and 3 patients with severe hepatic impairment (total bilirubin > 3x ULN any AST). Within this cohort, no clinically meaningful differences were identified in the incidence of treatment-emergent adverse events (TEAEs) or serious adverse events (SAEs).

Furthermore, Study 027 was conducted with primary objectives to evaluate the impact of hepatic impairment on the pharmacokinetics, anti-tumor activity, and tolerability of selinexor. An interim Clinical Study Report (CSR) from Study 027 now provides pharmacokinetic (PK) and safety results for patients with normal hepatic function, mild hepatic impairment (MHI), and severe hepatic impairment (SHI) following the administration of single-agent selinexor. The results of Study 027 demonstrated that selinexor exposure is minimally affected by moderate hepatic impairment, with dose-normalized free drug levels remaining within 10 % of normal, thus requiring no dose adjustment. However, severe hepatic impairment leads to a significant increase in dose-normalized total and free selinexor exposure (up to 32 % and 41 % respectively), driven by reduced clearance. Given the compound's steep exposure-safety

relationship, a conservative dose reduction is proposed for patients with severe hepatic impairment to mitigate the risk of increased toxicity and match exposures seen in patients with normal hepatic function.

Is it considered to be included as missing information? No

Rationale: There are no known or expected safety concerns for use in the target population.

Non-adequate renal function

Reason for exclusion: Selinexor is not significantly metabolized by the kidney, nor was renal dysfunction expected to significantly affect selinexor distribution, side effects or antitumor activity. However, to avoid confounding factors for data analyses, only patients with estimated creatinine clearance of ≥ 20 mL/min by Cockroft and Gault (i.e., moderately severe to severe) in the 3 weeks prior to first dose were to be included in the clinical development program. A total of 28 patients with a creatinine clearance ≥20 and < 30 mL/min (severe renal dysfunction) were included in the HM-Pool; no clinically meaningful differences in the incidence of Grade 3/4 TEAEs/related TEAEs (TRAEs) or SAEs were identified in this group compared to the overall pool.

Is it considered to be included as missing information? Yes

Rationale: Not applicable as included under missing information.

Active, unstable cardiovascular function

Reason for exclusion: To ensure patient safety and to avoid confounding factors for data analyses, active, unstable cardiovascular function, i.e. symptomatic ischaemia, or uncontrolled clinically-significant conduction abnormalities, or congestive heart failure of New York Heart Association (NYHA) Class ≥3, or myocardial infarction within 3 months prior to first dose were excluded from the clinical development program.

Is it considered to be included as missing information? No

Rationale: To avoid confounding factors for study analyses and to ensure that patients are able to participate in all study procedures. There are no known or expected safety concerns for use in the target population.

Non-adequate hematopoietic function

Reason for exclusion: Patients with a total WBC count < 1,000/mm^3, an absolute neutrophil count < 1000/mm^3, a platelet count < 75,000/mm^3 (patients in whom < 50 % of bone marrow nucleated cells are plasma cells) or < 50,000/mm^3 (patients in whom ≥ 50 % of bone marrow nucleated cells are plasma cells within 3 months prior to first dose were excluded from the clinical development program to avoid confounding factors for efficacy and safety analyses.

Is it considered to be included as missing information? No

Rationale: There are no known or expected safety concerns for use in the target population.

ECOG Status score of > 2.

Reason for exclusion: In order to ensure that patients would be able to participate in all study related office visits and procedures, only patients with an ECOG performance status ≤ 2 were included in the clinical development program.

Is it considered to be included as missing information? No

Rationale: The exclusion of patients with poorer performance status was for procedural (study conduct) rather than specific safety reasons. No specific safety issues are expected in patients with ECOG Status > 2, although increased attention to weight maintenance, caloric and fluid intake and general health status would be recommended for these patients.

Prior malignancy that required treatment or has shown evidence of recurrence during the 5 years prior to randomisation.

Reason for exclusion: Prior malignancies within 5 years of the study were excluded to avoid confounding of efficacy results including overall survival as the studies focused on RRMM.

Is it considered to be included as missing information? No

Rationale: There are no known or expected safety concerns for use in the target population.

Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within 1 week prior to first dose.

Reason for exclusion: To ensure patient safety and to avoid confounding factors for safety analyses, as well as to ensure that patients would be able to participate in all study related procedures, selinexor treatment was delayed in patients with clinically unstable, severe infections. When the patients were medically stabilized, patients could resume selinexor dosing even while receiving anti-microbial agents.

Is it considered to be included as missing information? No

Rationale: To avoid confounding safety analyses, ensure patient safety and to ensure adequate patient compliance. There are no known or expected safety concerns for use in the target population.

Active plasma cell leukaemia.

Reason for exclusion: Although related to MM, this is a distinct entity with unique biology and treatment. Treatment of plasma cell leukaemia is typically multi-agent chemotherapy and not single agent therapy. This represents a distinct malignancy and therefore would confound efficacy and safety information.

Is it considered to be included as missing information? No

Rationale: Use of single agent selinexor in patients with active plasma cell leukaemia is not intended.

Documented systemic light chain amyloidosis.

Reason for exclusion: This is a different disease with unique biology, end organ dysfunction including cardiac and / or renal dysfunction. The endpoints to assess response are also different than myeloma. The outcomes in patients with amyloidosis is very different than those without amyloidosis and therefore will impact efficacy outcomes. The high number and the nature of AEs associated with the condition are expected to interfere with the safety signal detection in clinical studies.

Is it considered to be included as missing information? No

Rationale: The unique biology and severe nature of systemic light chain amyloidosis would impact the safety and efficacy analysis. There are no known or expected safety concerns for use in the target population.

MM involving the central nervous system.

Reason for exclusion: The outcomes in patients with CNS involvement is very different than those without CNS involvement and therefore will impact efficacy outcomes. The high number and the nature of adverse events (AEs) associated with these conditions are expected to interfere with the safety signal detection in clinical studies.

Is it considered to be included as missing information? No

Rationale: No major CNS toxicity was observed in clinical studies, the safety profile of selinexor is consequently not expected to be significantly different in patients with MM involving the CNS compared with patients without such involvement. However, the outcomes including efficacy analysis would be impacted.

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome.

Reason for exclusion: This is a distinct entity from MM. The high number and the nature of adverse events (AEs) associated with these conditions are expected to interfere with the safety signal detection in clinical studies.

Is it considered to be included as missing information? No

Rationale: There are no known or expected safety concerns for use in the target population.

Spinal cord compression.

Reason for exclusion: Spinal cord compression represents a neurological emergency requiring immediate and specific treatment which is different than that for RRMM. The high number and the nature of AEs associated with the condition are expected to interfere with the safety signal detection in clinical studies. To ensure that patients would be able to participate in all study related procedures and ensure compliance.

Is it considered to be included as missing information? No

Rationale: There are no known or expected safety concerns for use in the target population.

Greater than Grade 2 peripheral neuropathy or Grade ≥ 2 peripheral neuropathy with pain at baseline

Reason for exclusion: The high number and the nature of AEs associated with these conditions are expected to interfere with the safety signal detection in clinical studies.

Is it considered to be included as missing information? No

Rationale: There are no known or expected safety concerns for use in the target population.

Active graft versus host disease (after allogeneic stem cell transplantation)

Reason for exclusion: The severe nature of this condition is expected to interfere with study procedures. In addition, the high number and the nature of AEs associated with the condition are expected to interfere with the safety signal detection in clinical studies.

Is it considered to be included as missing information? No

Rationale: Procedural issues due to expected low patient compliance. To avoid confounding factors for safety analyses in the studies.

Body Surface Area < 1.4 m2 at baseline

Reason for exclusion: To ensure the patients with low BSA are safely dosed given the fixed dosing implemented in trials.

Is it considered to be included as missing information? No

Rationale: To avoid confounding factors for safety analyses in the studies.

Known active human immunodeficiency virus (HIV) infection or HIV seropositivity.

Reason for exclusion: The high number and the nature of AEs associated with these conditions are expected to interfere with the safety signal detection in clinical studies.

Is it considered to be included as missing information? No

Rationale: There are no known or expected safety concerns for use in the target population.

Known active hepatitis A, B, or C infection; or known to be positive for hepatitis C virus ribonucleic acid (RNA) or hepatitis B virus surface antigen.

Reason for exclusion: The high number and the nature of AEs associated with these conditions are expected to interfere with the safety signal detection in clinical studies.

Is it considered to be included as missing information? No

Rationale: There are no known or expected safety concerns for use in the target population.

Non-haematological toxicities > 1 or > 2 when a chronic toxicity is present.

Reason for exclusion: To avoid confounding factors for safety analyses in the studies.

Is it considered to be included as missing information? No

Rationale: These patients often have baseline G1-2 toxicities. It is not expected that the risk-benefit balance is changed in these patients compared to the overall target population.

Uncontrolled active hypertension

Reason for exclusion: Underlying active medical comorbidities that are not well controlled interfere with the safety signal detection in clinical studies.

Is it considered to be included as missing information? No

Rationale: There are no known or expected safety concerns for use in the target population.

Smouldering MM

Reason for exclusion: Smouldering MM is an early form of MM with high levels of monoclonal proteins, but no clinical signs or symptoms of frank MM. Selinexor is not intended for this condition.

Is it considered to be included as missing information? No

Rationale: Use of selinexor in smouldering MM is outside the intended indication for selinexor.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development program is unlikely to have detected rare adverse reactions or adverse reactions caused by prolonged exposure beyond 24 months.

A follow-up period of 1 year in the pivotal study KCP-330-012 permits the detection of AEs with a long latency. In the ongoing phase 3 Study KCP-330-023, patients will be monitored for delayed toxicities and survival for a 5-year period, regardless of whether or not they discontinued the study early.

As of the DLP, the longest duration of treatment with selinexor in clinical studies was 2,346 days. In total, 266 patients have remained on selinexor therapy for > 1 year, with 86 out of 266 patients for > 2 years,and no new evidence of cumulative toxicities have been detected.

As of April 2018, 40 patients in studies of patients with haematological malignancies have remained on selinexor therapy for ≥ 48 weeks, with 5 patients exposed to selinexor for > 2 years, with no clinically significant cumulative toxicities identified or potential signals detected. When patients in the MM-Pool were considered (*Table SIII - 7*), although the crude rate of occurrence of the most common TEAEs appeared to increase with increasing cumulative dose, when adjusted for duration of exposure (per 100 patients per 4-week cycle), the incidence rates of TEAEs, and treatment-related TEAEs, were stable, or an inverse relationship between incidence and cumulative dose was apparent. This indicates that the crude rate of occurrence of common TEAEs tends to increase only with time on study, rather than reflecting an association with the cumulative exposure (dose) of selinexor.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV - 1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women Breastfeeding women	No data are available on the use of selinexor in pregnant women. No pregnancies were reported in any of the selinexor studies. There is no information regarding the presence of selinexor in human milk, the effects on the breastfed infant, or the effects on lactation as these populations were not included in the clinical development program.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease intensity different from inclusion criteria in clinical trials	<u>Patients with hepatic impairment</u> Only patients with adequate hepatic function (here defined as total bilirubin < 2x ULN (for Gilbert's syndrome: total bilirubin of < 3x ULN), AST < 2.5x ULN and ALT < 2.5x ULN) in the 3 weeks prior to first dose were to be included in the clinical development program. In the HM-Pool (996 patients), 137, 11, and 3 patients with mild, moderate, and severe hepatic impairment, respectively, were included, with no safety signal identified. In Study 027, a total of 13 patients with hepatic impairment were enrolled: 7 with moderate and 6 with severe impairment. The results of the hepatic impairment monotherapy portion of Study 027 evaluating the potential impact of hepatic function on selinexor PK demonstrated that selinexor exposures were minimally altered in patients with MHI. The 24 % lower apparent clearance for total selinexor in SHI (29 % lower for free selinexor) and the corresponding increase in selinexor exposures suggest that SHI has a moderate impact on selinexor PK. Notably, the overall safety profile, including TEAEs, remained consistent with the drug's known safety profile across all hepatic function groups, no new concerns were identified within this sub-population. <u>Patients with renal impairment</u> Patients with estimated creatinine clearance of ≥ 20 mL/min in the 3 weeks prior to first dose were included in the clinical development program. This includes patients with mild (60 – 89 mL/min) and moderate (30-59 mL/min) renal impairment. A total of 28 patients with a creatinine clearance ≥20 and < 30 mL/min were included in the HM-Pool with no safety signal being detected. <u>Patients with cardiovascular impairment</u> Patients with active, unstable cardiovascular function, i.e. symptomatic ischaemia, or uncontrolled clinically-significant conduction abnormalities, or congestive heart failure of New York Heart Association (NYHA) Class ≥3, or myocardial infarction within 3 months prior to the first dose were excluded from the clinical development program.

Type of special population	Exposure
Pregnant women Breastfeeding women	No data are available on the use of selinexor in pregnant women. No pregnancies were reported in any of the selinexor studies. There is no information regarding the presence of selinexor in human milk, the effects on the breastfed infant, or the effects on lactation as these populations were not included in the clinical development program.
	Immunocompromised patients Human immunodeficiency virus (HIV)-positive patients were excluded from the clinical development program. Patients with a disease intensity different from inclusion criteria in clinical trials In MM studies, only patients with relapsed or refractory disease were included. Smoldering MM was usually excluded as was an Eastern Cooperative Oncology Group (ECOG) Performance Status of > 2.
Population with relevant different ethnic origin	Most patients (84 %) in CSTs were White, 6 % were Black or African American, and 3 % were Asian. Analysis of safety data for the HM-Pool and the MM-Pool by race did not identify clinically meaningful differences. Clinical exposure by ethnic origin is provided in *Table SIII - 2*.
Subpopulations carrying relevant genetic polymorphisms	Selinexor has not been evaluated in populations carrying any known and relevant polymorphisms that may affect the outcome of therapy.

PART II: MODULE SV. POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

Xpovio® (selinexor) received accelerated approval by the FDA on 03 July 2019, for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal. Xpovio® (selinexor) also received accelerated approval by the FDA on 22 June 2020, for the treatment of adult patients with relapsed or refractory DLBCL, not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy. Xpovio® (selinexor) also received full approval by the FDA on 18 December 2020 in combination with bortezomib and dexamethasone for the treatment of adult patients with MM who have received at least 1 prior therapy.

Nexpovio® (selinexor) received conditional marketing authorization by the European Union on 26 March 2021, and is indicated in combination with dexamethasone for the treatment of MM in adult patients who have received at least 4 prior therapies and whose disease is refractory to at least 2 PIs, 2 IMiDs and an anti-CD38 mAb, and who have demonstrated disease progression on the last therapy. Full marketing authorization was granted on 18 July 2022, in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

SV.2 Method used to calculate exposure.

In the US, about 45 % of data comes through specialty pharmacies with unique patient identification number which is used to calculate total number of patients who started the therapy and their refills rates. The remaining 55 % of data comes from specialty distributors.

SV.3 Exposure

Cumulatively, as of 25 March 2025, approximately 15,556 patients have received selinexor in a commercial setting in the United States (US).

Selinexor was first launched in the EU in Germany in October 2022, in Austria on 21 December 2022, in France on 15 October 2024 and in Italy on 18 December 2023 for use in second-line and penta-refractory multiple myeloma. As each unit corresponds to a 4-week pack, cumulative PM exposure has been 276 patient-years or an estimated 1,795 patients until 25 March 2025.

PART II: MODULE SVI. ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes
Based on its mechanism of action and safety profile, selinexor is not considered to have abuse potential. The development of drug dependence is not expected.

PART II: MODULE SVII. IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:
Most adverse drug reactions in the relevant clinical studies were mild or moderate in intensity, reversible with dose modifications and / or supportive care and did not lead to drug discontinuation. Therefore, selinexor is considered to be generally well tolerated and have insignificant impact on patients in relation to the severity of the indication, triple class refractory MM, treated. Reasons for not including very common (≥ 10 % of patients in the MM-Pool) and common (≥ 1 % of patients) related AEs from the MM-Pool in the list of important identified risks are provided below.

- Risks, i.e., common expected adverse reactions reported in patients with heavily pre-treated multiple myeloma (MM-Pool) according to the SmPC with minimal clinical impact on patients (in relation to the severity of the indication treated):

  Anaemia, Nausea, Vomiting, Constipation, Abdominal Pain, Diarrhoea, Dizziness, Dyspepsia, Dry mouth, Abdominal discomfort, Pyrexia, Asthenia, Malaise, Gait disturbance, General physical health deterioration, Chills, Alopecia, Night sweats, Dyspnoea, Epistaxis, Cough, Muscle spasms, Muscular weakness, Bone pain, Hypercreatinaemia, Hypocalcaemia, Hypophosphataemia, Hypomagnesaemia,

Hyperkalaemia, Hyperamylasaemia, Hyperlipasaemia, Hyperuricaemia, Dehydration, Hypokalaemia, Hyperglycaemia, Dysgeusia, Headache, Hypotension, Insomnia, Anxiety, Fall.

In addition, delirium and depression are commonly associated with both the underlying disease, old age, and the use of glucocorticoids.

- Known risks that do not impact the risk-benefit profile.
  Peripheral neuropathy, Syncope, Tachycardia
- Adverse reactions with clinical consequences, even serious, but occurring with a low frequency (uncommon) and considered to be acceptable in relation to the severity of the indication treated:
  Encephalopathy
- Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):

Dehydration was a very common adverse reaction in clinical studies, usually occurring in association with gastrointestinal effects like decreased appetite, nausea, vomiting, and diarrhoea. SmPC Section 4.4 states: Selinexor plus low-dose dexamethasone can cause nausea, vomiting and diarrhoea. Selinexor requires prophylactic use of 5-HT3 antagonists or similar anti-nausea agents. Fluids with electrolytes should be administered to prevent dehydration in patients at risk. The wording in SmPC is considered sufficient.

Fatigue was experienced frequently by patients in the target population in clinical trials. Fatigue remains commonly associated with other commonly reported side effects of selinexor such as decreased appetite, anaemia, weight decreased, and dehydration. Prevention of anorexia, vomiting, and dehydration may reduce Fatigue. Fatigue is manageable through dose modifications, including dose interruptions and dose reductions. Fatigue has been sufficiently characterised and is managed through appropriate labelling.

Decreased appetite was experienced frequently by patients in the target population in clinical and non-clinical trials. SmPC Section 4.4 states: selinexor can cause weight loss and anorexia. Patients should have their body weight, nutritional status and volume checked at baseline, during treatment, and as clinically indicated. Monitoring should be more frequent during the first two months of treatment. Patients experiencing new or worsening decreased appetite and weight may require dose modification, appetite stimulants, and nutritional consultations. Decreased appetite has been sufficiently characterised and is managed through appropriate labelling.

Weight decreased was experienced frequently by patients in the target population in clinical and non-clinical trials. SmPC Section 4.4 states: Selinexor can cause weight loss and anorexia. Patients should have their body weight, nutritional status and volume checked at baseline, during treatment, and as clinically indicated. Monitoring should be more frequent during the first two months of treatment. Patients experiencing new or worsening decreased appetite and weight may require dose modification, appetite stimulants, and nutritional consultations. Weight decreased has been sufficiently characterised and is managed through appropriate labelling.

Hyponatremia events indicative of Hyponatraemia were experienced frequently by patients in clinical trials. Hyponatraemia in patients receiving selinexor was manageable with supportive care, adjustment of concomitant medications, and dose modifications. SmPC Section 4.4 states: selinexor can cause hyponatraemia. Patients should have their sodium levels checked at baseline, during treatment, and as clinically indicated. Monitoring should be more frequent during the first two months of treatment. Correct sodium levels for concurrent hyperglycaemia (serum glucose > 150 mg/dL) and high serum paraprotein levels. Hyponatraemia should be treated as per medical guidelines (intravenous sodium chloride solution and / or salt tablets), including dietary review. Hyponatraemia has been sufficiently characterised and is managed through appropriate labelling.

Confusional state events indicative of confusion were experienced frequently by patients in the target population in clinical trials. SmPC Section 4.4 states: Selinexor can cause confusional state and dizziness. Patients should be instructed to avoid situations where dizziness or confusional state may be a problem and to not take other medicinal products that may cause dizziness or confusional state without adequate medical advice. Patients should be advised not to drive or operate heavy machinery until symptoms resolve. Confusional state has been sufficiently characterised and is managed through appropriate labelling.

Tumour lysis syndrome this risk is considered to be well characterized and addressed in the SmPC sections 4.4 and 4.8. Section 4.4. of the SmPC states: Tumour lysis syndrome (TLS) has been reported in patients receiving therapy with selinexor. Patients at a high risk for TLS should be monitored closely. Treat TLS promptly in accordance with institutional guidelines. Section 4.8 of the SmPC states: Tumour lysis syndrome (TLS) occurred in one (< 1 %) patient (who received Sd) which was considered Grade 3 and serious. Patients at a high risk for TLS should be monitored closely. Treat TLS promptly in accordance with institutional guidelines (see section 4.4).

- Other reasons for considering the risks not important:

Hepatic Adverse Events (including Alanine aminotransferase increased, Aspartate aminotransferase increased):
Patients in both the HM-Pool and the MM-Pool had advanced, heavily pre-treated, relapsed/refractory malignancies, and > 10 % of patients in the HM-Pool had baseline abnormalities in ALT. Despite these characteristics, TEAEs of hepatic dysfunction (by SOC) were infrequently encountered among patients exposed to selinexor: 2.2 % in the MM-Pool, regardless of relationship. Few patients (0.7 %) required dose modifications because of hepatobiliary events and only 3 patients discontinued treatment. The overall incidence of hepatobiliary SAEs was also low: 1.2 % in the HM-Pool and 0.7 % in the MM- Pool. The majority of patients with SAEs in the hepatobiliary disorders SOC had pre- existing chronic liver disease and intercurrent events, such as transient biliary obstruction associated with cholelithiasis or cholangitis and did not present clinical pictures concerning for drug-related hepatic toxicity. Analyses of biochemical tests of liver function (e.g. transaminases) did not identify any consistent trends over time or across dose groups, either in absolute values or change from baseline. No cases met Hy's Law criteria.

Based on review of the AE and biochemical data from the HM-Pool and the MM-Pool, and consistent with the nonclinical toxicology studies, there is no evidence suggestive of a signal of hepatotoxicity with selinexor.

Renal Adverse Events (including Hypercreatininaemia, Acute Kidney injury):

The majority of renal impairment Standard MedDRA query (SMQ) events in the HM-Pool and MM-Pool were non-serious increases in serum creatinine that were either Grade 1 or 2, and most were reversible with standard interventions. Given the age, comorbidities and nature of the malignancies of the patients studied, together with the previous multiple oncological treatment regimens, these events are likely attributable to increased susceptibility to the effects of volume depletion, hypotension, or other factors acting on kidneys with limited or no reserve and diminished autoregulatory capacity due to intrinsic renal damage from comorbid conditions, MM itself, and prior therapies. For example, in some cases, renal dysfunction was exacerbated by the effects of diuretics, non-steroidal anti-inflammatory agents and ACE inhibitors.

Approximately 27 % of patients in the HM-Pool ([267/996]) and 31 % of patients in the MM-Pool ([170/552]) had moderate or severe chronic renal impairment at baseline, based on estimated creatinine clearance. In this context, even mild volume depletion, whether due to inadequate intake from reduced appetite or nausea, or fluid losses from vomiting or diarrhoea, is enough to reduce renal perfusion and impair creatinine and urea clearance leading to prerenal azotaemia and not intrinsic renal damage. This interaction of clinical factors is also apparent in the renal impairment SAEs, some of which only required hospital admission for intravenous fluid administration.

A trend for the marginally higher incidence and intensity of events in the MM population, at least when MM patients in the HM-Pool were compared with the entire HM-Pool, is consistent with the kidney being a target organ in MM, particularly in patients with advanced, heavily pretreated disease of long duration.

The reversibility of hypercreatininaemia (median duration of hypercreatininaemia TEAEs in the HM-Pool was 11 days), the comparatively low incidence of events of acute kidney injury (AKI) (and its synonyms), and low rates of discontinuations due to renal events, suggest the lack of a direct nephrotoxic effect of selinexor.

The absence of a positive relationship between total dose and incidence of renal impairment SMQ events further supports this view. The more frequent occurrences of events at twice weekly doses of selinexor at doses of 100 mg or greater is consistent with greater incidences of anorexia, vomiting, dehydration and diarrhoea and lesser tolerability of higher doses studied earlier in clinical development and that will not be carried forward. In addition, there is no apparent effect of renal dysfunction itself on the dosing of selinexor, and this agent can be used in patients with moderately severe and even severe renal failure.

The SAEs of AKI of grade ≥3 typify AKI in patients with any heavily pretreated hematologic malignancies: the patients have susceptibilities such as advanced age, pre- existing renal impairment from comorbidities and multiple previous oncological treatment regimens and have reached the advanced and terminal stages of malignancies. The associated intercurrent infections, sepsis and multi-organ failure invariably have a detrimental effect on kidney function. As with the nonserious elevations in creatinine, these SAEs do not suggest that selinexor has a direct nephrotoxic effect.

Eye disorders (including Cataract, Vision blurred, Visual impairment)

Ocular TEAEs were reported by 24.2 % patients in the HM-Pool and 25.4 % in the MM-Pool. The frequencies were consistent between the pools, indicating that underlying malignancy and different dosing regimens, including single agent selinexor or in combination with other antimyeloma drugs, had no influence on occurrence of ocular TEAEs overall.

The findings of an independent ophthalmologic expert are summarised below:

Based upon the screening examination data, it is evident that the patients entered the trials with typical ophthalmic age-related changes, especially lens changes. Hence, any conclusions about ophthalmic safety concerns have to be evaluated against a background of ocular findings commonly encountered in this age group.

Vision blurred (13.7 % in HM-Pool; 13.6 % in MM-Pool), cataract (3.4 % in HM-Pool; 5.3 % in MM-Pool), visual impairment (2.5 % in HM-Pool; 2.5 % in MM-Pool), dry eye (1.6 % in HM-Pool; 2.7 % in MM-Pool), photopsia (1.2 % in HM-Pool; 1.3 % in MM-Pool), and visual acuity reduced (1.1 % in HM-Pool; 0.5 % in MM-Pool) were the most commonly reported events.

Frequencies of serious ocular events were low in both pools (0.8 % in the HM-Pool and 1.4 % in MM-Pool. The serious ocular event with the highest occurrence was cataract at 0.5 % in HM-Pool and 0.7 % in MM-Pool.

Based on pooled study data, the Expert Ophthalmological Opinion and the nonclinical studies, it was concluded that blurred vision, typically self-limited and without objective ophthalmological findings, can be caused by selinexor; about 2 % of the patients with ocular events reported blurred vision without an ophthalmological finding. Selinexor could usually be continued while blurred vision was evaluated in this population. Objective ocular changes were generally not associated with selinexor, as the most common ocular pathology, namely cataracts, occurred at the expected rate for the age of the population.

Selinexor could be given prior to and shortly after cataract surgery without apparent negative outcomes.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk 1: Thrombocytopenia and Bleeding

Risk-benefit impact:
In the selinexor development program, dose-limiting toxicities (DLTs) of thrombocytopenia have been observed. Thrombocytopenia was experienced frequently by patients in the target population in clinical trials. Bleeding events were observed in few patients with thrombocytopenia; most of the events including epistaxis, contusion, haematuria and petechiae, were mild or moderate in severity. Grade 3 or 4 thrombocytopenia was not typically associated with bleeding. When assessing the contribution of selinexor to the development of individual cases of thrombocytopenia, multiple confounding variables including baseline thrombocytopenia, bone marrow cellularity, disease indication, patient age, previous treatments, advanced disease, current comorbidities, concomitant medications, and the complexity of the patient populations have to be considered.

Thrombocytopenia can be managed with dose interruption of selinexor, when appropriate, as well as dose reduction and change in schedule to once weekly administration, with the goal of maintaining antineoplastic activity. These actions may result in recovery of platelet counts in 1 to 3 weeks. In addition, thrombopoietin agonists, particularly romiplostim at moderate to high doses, have improved platelet counts in heavily pre-treated patients with MM receiving

selinexor, permitting continued dosing of selinexor and thus maintaining antineoplastic effects.

Important Identified Risk 2: Severe infections due to Neutropenia

Risk-benefit impact:
Clinical trial data indicated that while treatment-emergent neutropenia events following selinexor administration were relatively frequent, grade ≥3 neutropenia occurred in < 30 % of MM patients despite their underlying disorders and prior therapies. There was no clear dose-response relationship with selinexor, and little to no impact on selinexor administration in terms of discontinuations, modifications, or interruptions due to neutropenia TEAEs. Severe infections due to neutropenia were observed in clinical trials, the most commonly reported infectious events that occurred concurrently with neutropenia (defined as +/- 5 days of onset of neutropenia event), were pneumonia, lung infection, sepsis, urinary tract infection, bacteraemia,and influenza (MM Pool). Lastly, febrile neutropenia events associated with selinexor were relatively infrequent (3.6 % of patients in the MM Pool). With appropriate monitoring and management, neutropenia and related infections have minimal impact on the risk-benefit assessment of selinexor.

Important Potential Risk1: Acute cerebellar syndrome

Risk-benefit impact:
Acute cerebellar syndrome (ACS) was uncommonly reported (1 adult patient with heavily pretreated, relapsed pancreatic cancer and baseline cerebellar abnormalities on magnetic resonance imaging (MRI) who was treated with selinexor 145 mg twice weekly (i.e., a very high dose which is no longer used); 2 cases occurred in pediatric patients with refractory AML, also with baseline cerebellar abnormalities and treated at very high doses which are no longer used). There are no reported cases of ACS in adults with hematologic malignancies including MM, and the three cases above are the only cases reported in 3111 patients treated with selinexor alone or in combination with other anti-neoplastic agents in clinical studies as of March 31, 2019. in addition, there have been no reported cases of ACS in the initial post-marketing experience of selinexor in USA. However, because ACS can be associated with significant morbidity and there are direct implications for monitoring and management, ACS has been characterised as an important potential risk of selinexor.

Important Potential Risk 2: Medication errors

Risk-benefit impact:
Although PTs of Medication Error (ME) were not reported in HM-Pool or MM-Pool patients, Overdose (SOC Injury, poisoning and procedural complications) was reported in 3 and 5 patients in HM-Pool and MM-Pool respectively; with one patient belonging to both HM-Pool as well as MM-Pool. Considering the potential unintended consequences following medication errors in particular due to overdose ME has been recognized as an important potential risk of selinexor.

Missing information 1: Use in patients with severe renal impairment

Risk-benefit impact:
Patients with severe renal impairment (creatinine clearance < 20 mL/min) were generally excluded from clinical trials. Nevertheless, a total of 28 patients with a creatinine clearance ≥20 and < 30 mL/min were included in the HM-Pool with no safety signal being detected.

Use in patients with severe renal impairment is included under missing information with the objective of accumulating additional knowledge on this topic.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

There are no new safety concerns, however the missing information "use in patients with severe hepatic impairment" has been removed from the RMP based on the study results from KCP-330-027. This study evaluated patients with moderate hepatic impairment (MHI) and severe hepatic impairment (SHI), characterizing the relationship between hepatic function and Selinexor PK. This risk is considered as well characterized and results of the study and corresponding starting dose recommendations are proposed for inclusion in the SmPC section 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties and in the Patient Information Leaflet (PIL) section 3.

Reasons for removal from list of safety concerns: The above safety concern no longer meets the definition of a safety concern and does not require additional PV activities. While the data suggested no increase in exposure in patients with MHI/SHI, in order to protect patient safety, a lower starting dose was recommended to be used in this population.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important Identified Risk 1: Thrombocytopenia (including the PTs Thrombocytopenia and Platelet count decreased) and Bleeding.

Potential mechanisms:
Thrombocytopenia is a frequent adverse reaction to anti-neoplastic agents, particularly in patients with hematologic malignancies that have been previously treated (*Lonial et al., 2005*). The effects of selinexor on platelet generation are related to a slowing of maturation of megakaryocytes and a reduction in their average ploidy (*Machlus, 2017*). Selinexor also has been seen to reversibly affect platelet formation (*Machlus et al., 2014*).

Evidence source(s) and strength of evidence:
In the selinexor development program, DLTs of thrombocytopenia have been observed. Thrombocytopenia was observed frequently by patients in the target population in clinical trials. Almost half of the patients with events in completed trials had thrombocytopenia of Grade ≥ 3 and one patient died from bleeding due to thrombocytopenia considered possibly related to selinexor treatment.

Characterisation of the risk:
TEAEs of thrombocytopenia were reported in 555 (55.7 %) patients in the HM-Pool. Although the majority were non-serious, Grade ≥ 3 TEAEs were reported in 455 (45.7 %) patients. 161 (16.2 %) patients had Grade 3 thrombocytopenia, 294 (29.5 %) had Grade 4, and none was Grade 5. Three hundred eighty-seven (38.9 %) had a Grade 3/4 TRAE. When laboratory data were reviewed, of 466 patients in the HM-Pool who had a worst on study platelet count of Grade 4, 126 were Grade 4 at baseline, 93 were Grade 3 at baseline, 55 were Grade 2 at baseline and 110 were Grade 1 at baseline.

SAEs of thrombocytopenia were reported in 24 (2.4 %) patients of which 17 (1.7 %) patients had TRSAEs. None of the patients had a fatal event of thrombocytopenia. Most patients did

not receive treatment for the TEAE of thrombocytopenia. 182 patients (18.3 %) had a TEAE leading to dose modification and for 24 patients (2.4 %) the event led to study drug discontinuation. Generally, patients who received supportive care were those with a TEAE Grade ≥ 3; supportive care included platelets (70 patients; 12.6 %), romiplostim (41 patients; 7.4 %), eltrombopag (35 patients; 6.3 %), tranexamic acid (9 patients; 1.6 %), plasma transfusions (4 patients; < 1 %), and oprelvekin (3 patients; < 1 %).

Of the 62.7 % (346/552) patients in the MM-Pool who had at least 1 TEAE of thrombocytopenia, 2.2 % (12/552) had events that led to discontinuation of selinexor and 30.4 % (168/552) had events that led to a reduction or interruption in selinexor dosing. Of the 168 patients with a dose reduction or interruption, 21.2 % (117/552) continued to receive selinexor after the event. Of these 117 patients, 15.4 % (18/117) had no recurrence of thrombocytopenia, 15.4 % (18/117) had a recurrence of thrombocytopenia of a lower intensity (i.e., lower grade), and 69.2 % (81/117) had a recurrence of thrombocytopenia at the same or higher intensity (i.e., ≥ the grade of initial event).

TEAEs of thrombocytopenia were infrequently associated with Grade ≥ 3 bleeding events in the HM-Pool. Of the 555 patients with at least 1 TEAE of thrombocytopenia, concurrent bleeding events (concurrency defined as ± 5 days) of Grade 3 or higher were reported in 26 (5.7 %; 26/555) patients. Bleeding events by PT included: epistaxis (7 patients), gastrointestinal haemorrhage (5 patients), rectal haemorrhage (2 patients), cerebral haemorrhage (2 patients), haemorrhage intracranial (2 patients), subdural haematoma (2 patients), CNS haemorrhage (2 patients), and events in 1 patient each included contusion, haematuria, haematoma, purpura, haemorrhoidal haemorrhage, haematochezia, eye haemorrhage, tumor haemorrhage, and procedural haemorrhage.

Most of the bleeding events were Grade 3, with Grade 4 event in 1 patient and Grade 5 events in 6 patients. For one of the 6 patients dying from a bleeding event, the event (cerebral haemorrhage) was considered possibly related to selinexor treatment by the investigator; of note, this patient was also receiving anti-platelet therapy. A Grade 4 treatment-related event of hematochezia was reported in 1 patient with AML. However, this individual had a history of Clostridium difficile and Grade 4 thrombocytopenia at baseline. Hematochezia resolved after treatment with tranexamic acid, platelet transfusions and proton-pump inhibitor therapy.

As of 18 Feb 2020, in BOSTON study, the TEAE of thrombocytopenia was reported in 117 (60.0 %) patients in the SVd arm. Fifty-six (28.7 %) patients had Grade 3 and 21 (10.8 %) patients had Grade 4 thrombocytopenia. Three (1.5 %) patients had an SAE of thrombocytopenia. While 76 (39 %) patients had dose modifications due to thrombocytopenia, only 4 patients (2.1 %) discontinued study treatment.

Among the patients with Grade ≥ 3 thrombocytopenia, clinically significant (Grade ≥ 3) bleeding events were reported in 4 (5.2 %) of the 77 patients in the SVd arm. Grade ≥ 3 bleeding events reported in 4 patients in the SVd arm were epistaxis (2 patients), upper gastrointestinal haemorrhage / haemorrhagic shock (1 patient) and cerebral hemorrhage.

The incidence of new-onset thrombocytopenia in the SVd arm remained consistent over time without any increase with long-term treatment. However, in the SVd arm, new-onset Grade 4 thrombocytopenia fell progressively from 14 % (Days 1 to 56), to 13 % (Days 57 to 168), to 4 % (> Day 168). Thus, while there was evidence of reversible effects of selinexor on the megakaryocytes, there was no evidence of cumulative toxicity.

<u>Risk factors and risk groups:</u>

Assessment of the contribution of selinexor to the development of thrombocytopenia in the patients under study was influenced by multiple confounding variables including baseline thrombocytopenia, bone marrow cellularity, disease indication, patient age, previous treatments, advanced disease, current comorbidities, concomitant medications and the complexity of the patient populations studied (*Bishton et al., 2011*; *Liebman et al., 2014*; *Matsuoka et al., 2007*).

Preventability:
TEAEs of thrombocytopenia were usually managed with platelet transfusions, romiplostim, eltrombopag and less often managed with tranexamic acid, and oprelvekin. In the HM-Pool the median duration of thrombocytopenia TEAEs was significantly shorter in patients who received any supportive care within 5 days of event onset (12.7 days) as compared to patients who did not receive any supportive care within 5 days (21.0 days). The median duration of thrombocytopenia TEAEs in patients treated with platelet transfusion within 5 days was only 6.5 days.

In BOSTON study thirty-five (29.3 %) patients in the SVd arm received TPO receptor agonists. The median duration of Grade 3/4 thrombocytopenia was shorter (9.4 days) in patients who received TPO receptor agonists versus the patients who did not (11.8 days). Importantly, the median duration of selinexor treatment after the first Grade 3/4 event of thrombocytopenia was substantially longer in patients who received TPO agonists (157.5 days) versus patients who did not receive them (79 days). In addition, patients receiving TPO receptor agonists that experienced Grade 3/4 thrombocytopenia were less likely to have a subsequent thrombocytopenia event of the same grade or higher compared to those that did not receive supportive care: 50.0 % (11 patients out of 22) versus 64.1 % (25 patients out of 39).

Patients taking selinexor in combination with low-dose dexamethasone for MM should have their complete blood counts assessed at least monthly. Dose interruption and / or reduction and / or schedule modification may be required in case of thrombocytopenia.
Hematochezia resolved after treatment with tranexamic acid, platelet transfusions and proton-pump inhibitor therapy.

Impact on the risk-benefit balance of the product:
Bleeding associated with thrombocytopenia in patients exposed to selinexor has been infrequently reported. Thrombocytopenia can be managed with dose interruption of selinexor, when appropriate, and may lead to return of platelet counts in 1 to 3 weeks; as well as dose reduction and change in schedule to once weekly administration (while attempting to maintain antineoplastic activity). In addition, thrombopoietin agonists, particularly romiplostim at moderate to high doses, and platelet transfusions have improved platelet counts in heavily pre-treated patients with MM receiving selinexor, permitting continued dosing of selinexor and thus maintaining antineoplastic effects.

Despite the addition of a PI, IMiD or daratumumab, all of which also cause thrombocytopenia, to selinexor, the incidence of thrombocytopenia is not higher in the combinations in patients with MM. This provides evidence supporting the view that selinexor, in combination with other therapeutics for MM, does not lead to increased thrombocytopenia. In addition, the highly potent anti-MM activity of the combinations may improve the function and / or numbers of marrow megakaryocytes.

Public health impact:
The clinical study population is considered representative of the general population eligible for selinexor plus dexamethasone treatment. It is therefore expected that in the post-marketing setting the number of events of thrombocytopenia will be similar to the clinical study population. The potential impact on public health is considered low given the limited population intended to receive treatment.

Important Identified Risk 2: Severe infections due to Neutropenia (including the PTs Neutropenia and Neutrophil count decreased)

Potential mechanisms:
Selinexor, through its mechanism of action, has reversible effects on the maturation of bone marrow elements. This effect is frequently exacerbated in patients with malignancies occupying the bone marrow and in patients who have received marrow-toxic chemotherapy. Neutropenia is a frequent AE of anti-neoplastic agents, particularly in patients with hematologic malignancies that have been previously treated (*Palumbo et al., 2012*). Neutropenia can increase the risk of infections in these heavily pre-treated patients with underlying hematological malignancy. Infections are common in patients with advanced hematological malignancies due to the underlying cytopenia secondary to malignancy, various anti-neoplastic treatments, advanced age and associated co-morbidities.

Evidence source(s) and strength of evidence:
Neutropenia was experienced frequently by patients in the target population in clinical trials. About 30 % of the patients had neutropenia at some point of treatment and most cases were Grade 3 events. Neutropenia considered related to selinexor treatment was reported for about a quarter of the patients. Severe infections due to neutropenia were observed in clinical trials, the most commonly reported infectious events occurring concurrently with neutropenia (defined as +/- 5 days of onset of neutropenia event), were pneumonia, lung infection, sepsis, urinary tract infection, bacteraemia, and influenza (MM Pool). Although neutropenia is not considered to be a risk factor for viral infections, the information is presented here in the context of neutropenia and infections.

Characterisation of the risk:
TEAEs of neutropenia were frequently reported (278 patients; 27.9 %) in the HM-Pool that included 28.4 % of MM patients, 30.9 % of AML patients, and 40.7 % of patients with other hematologic cancers. Although SAEs of neutropenia were infrequent (10 patients; 1.0 %), Grade ≥ 3 TEAEs were reported in 217 (21.8 %) patients, of which 117 (11.7 %) patients had Grade 3 and 100 (10.0 %) patients had Grade 4 events; none was Grade 5. One-hundred seventy-two (17.3 %) patients had a Grade 3/4 TRAE.

Of 295 patients in the HM-Pool who had a worst on study neutropenia of Grade 4, 125 were Grade 4 at baseline, 41 were Grade 3 at baseline, 32 were Grade 2 at baseline and 19 were Grade 1 at baseline. None was fatal and 8 patients (< 1 %) had treatment-related SAEs (TRSAEs). Duration-adjusted incidence rates per 100 patients per 4-week cycle of neutropenia TEAEs and TRAEs were 21.95 and 17.50, respectively, and those of SAEs and treatment-related SAEs were 0.31 and 0.24, respectively.

Of the 278 HM-Pool patients with a TEAE of neutropenia, the 3 most often reported types of concurrent infections (any grade, ≥ Grade 3) were pneumonia (17 patients, 6.1 %; 13 patients, 4.7 %), upper respiratory infection (15 patients; 5.4 %, 2 patients, 0.7 %), and urinary tract infection (13 patients; 4.7 %, 2 patients, 0.7 %).

In the MM-Pool, duration-adjusted incidence rates of TEAEs and TRAEs of febrile neutropenia were 1.87 and 1.12 per 100 patients per 4-week cycle respectively.

In MM-Pool (N = 552), TEAEs of neutropenia were reported in 185 (33.5 %) patients, Grade 3 in 97 (17.6 %) and Grade 4 in 42 (7.6 %) patients. No Grade 5 events were reported. TRAEs of neutropenia were reported in 163 (29.5 %) patients. One patient (0.2 %) had a SAE of neutropenia reported. Among the 185MM-Pool patients with TEAEs of neutropenia, 28 (15.1 %) patients had ≥ grade 3 infections and most common reported types of concurrent infections (any grade, Grade ≥ 3) were pneumonia (7.6 %, 4.3 %), upper respiratory tract infection (6.5 %, 0.5 %), and lung infection (4.9 %, 3.8 %). Only one patient had fatal infection (pneumonia) concurrently with neutropenia, however this patient had only grade 2 neutropenia. Opportunistic infections including fungal infections were uncommon. Most infections were not associated with neutropenia and were caused by non-opportunistic organisms.

As of 18 Feb 2020, in BOSTON study, 30 (15.4 %) patients in the SVd arm had at least 1 TEAE of neutropenia. There was 1 case of febrile neutropenia. Among the 30 patients on the SVd arm, 13 (6.7 %) had Grade 3 neutropenia, 5 (2.6 %) had Grade 4 neutropenia, and the remainder were Grade 1 or 2. Two (1.0 %) patients had an SAE of neutropenia, including the single case of Grade 4 febrile neutropenia. Seventeen (8.7 %) patients had dose modifications due to neutropenia as recommended in the dose reduction guidelines, but none had treatment discontinuation due to neutropenia.

In the SVd arm, 3 out of 18 patients with Grade ≥ 3 neutropenia had Grade ≥ 3 concurrent infection events that occurred within 5 days of ongoing neutropenia: 1 patient each with bronchitis, ear infection, and lower respiratory tract infection. The median time to onset of neutropenia was 44 days in the SVd arm. The median event duration was 8 days for the SVd arm. With long-term selinexor treatment, no consistent trends were observed in severity or median duration of new onset neutropenia events. This observation suggests that there was no cumulative myelotoxicity. Furthermore, there was minimal impact of neutropenic events on tolerability (i.e., continued selinexor dosing) and related clinically significant infections. Sixteen patients in the SVd received granulocyte colony stimulating factors (G-CSF) for neutropenia.

Risk factors and risk groups:
Main risk factors for the development of neutropenia in cancer patients are age, poor performance status, advanced disease, certain comorbidities (renal impairment, hepatic impairment, cardiovascular disease), low baseline blood cell counts, low body surface area / body mass index, treatment with myelosuppressive chemotherapies, and specific genetic polymorphisms (*Lyman et al., 2014).* Patients with advanced hematological malignancies are also at higher risk for infection due to the immune suppression from the underlying malignancy, poor performance status, low blood cell counts, prior anti-neoplastic treatments and multiple age related to co-morbidities.

Preventability:
Neutropenia can be managed with dose interruptions, modifications and colony-stimulating factors as per medical guidelines. Neutropenia required dose modification in 47 (4.7 %) patients and led to study drug discontinuation in 2 (0.2 %) patients.

Patients taking selinexor in combination with low-dose dexamethasone for MM should have their complete blood counts assessed at least monthly. A dose interruption and/or reduction and / or schedule modification may be required in case of treatment-emergent neutropenia.

Patients should be monitored for signs of infections, advise patients to inform if they have had a recent infection or get an infection. Consider supportive measures including antimicrobials for signs and symptoms of infection.

Impact on the risk-benefit balance of the product:
Clinical trial data indicated that while treatment-emergent neutropenia events following selinexor administration were relatively frequent, grade ≥ 3 neutropenia occurred in < 25 % of patients despite their underlying disorders and prior therapies. Majority of the concurrent infections were of lower grades and among the ≥ grade 3 infections, most common were pneumonia, upper respiratory infection and lung infection, which are known to occur at higher rates in patients with advanced heavily pre-treated haematological malignancies. There was no clear dose-response relationship with selinexor, and little to no impact on selinexor administration in terms of discontinuations, modifications, or interruptions due to neutropenia TEAEs. Lastly, febrile neutropenia events associated with selinexor were relatively infrequent.

Public health impact:
The clinical study population is considered representative of the general population eligible for selinexor plus dexamethasone treatment. It is therefore expected that in the post-marketing setting the number of events of neutropenia and infections associated with neutropenia will be similar to the clinical study population. The potential impact on public health is considered low given the limited population intended to receive treatment.

Important Potential Risk 1: Acute cerebellar syndrome

Potential mechanisms:
The exact mechanism of action associated with acute cerebellar syndrome is unknown.

Evidence source(s) and strength of evidence:
Using the cerebellar syndrome Customized MedDRA Query (CMQ) [a broad CMQ, created from noninfectious encephalitis Standardized MedDRA Query (SMQ) (broad search) by removing the following terms: coma neonatal, convulsion neonatal, convulsion in childhood on the ISS population, only 1 patient with evidence of cerebellar pathology was identified, but with clinical and radiographic features suggesting that the etiology is infectious or paraneoplastic in origin and not a manifestation of drug toxicity. In the remainder of the patients with event terms that may be associated with cerebellar involvement, the clinical pictures are representative of patients with advanced hematological malignancies, the lasting effects of previous treatments, multiple comorbidities and the risks of polypharmacy. Overall, there were 3 patients with ACS in the Selinexor development program. Acute cerebellar syndrome (ACS) was uncommonly reported (1 adult patient with heavily pretreated, relapsed pancreatic cancer and baseline cerebellar abnormalities on magnetic resonance imaging (MRI) who was treated with selinexor 145 mg twice weekly (i.e., a very high dose which is no longer used); 2 cases occurred in pediatric patients with refractory AML, also with baseline cerebellar abnormalities and treated at very high doses which are no longer used). As ACS can be associated with significant morbidity and there are direct implications for monitoring and management, ACS has been characterised as an important potential risk of selinexor.

Characterisation of the risk:
To date, only 1 case has occurred in an adult patient with heavily pretreated, relapsed pancreatic cancer and baseline cerebellar abnormalities on magnetic resonance imaging (MRI) who was treated with selinexor 145 mg twice weekly (i.e., a very high dose which is

no longer used); 2 cases occurred in pediatric patients with refractory AML, also with baseline cerebellar abnormalities and treated at very high doses no longer used. Overall, there were these 3 cases in > 3111 patients treated with selinexor alone or in combination with other anti-neoplastic agents in clinical trials. In addition, no cases of ACS have been reported in post-marketing surveillance in estimated > 500 patients treated with selinexor in USA following approval.

The one adult patient with evidence of cerebellar pathology was identified, but with clinical and radiographic features suggesting that the etiology is infectious or paraneoplastic in origin and not a manifestation of drug toxicity. In the remainder of the patients with event terms that may be associated with cerebellar involvement, the clinical pictures are representative of patients with advanced hematological malignancies, the lasting effects of previous treatments, multiple comorbidities and the risks of polypharmacy. ACS has not been reported in any adult patient with a hematologic malignancy, including MM, to date.

Based on a comprehensive review of the available data, a causal association between selinexor and ACS cannot be established.

Risk factors and risk groups:
Reported events ACS are often confounded by a variety of factors including central nervous system disorders due to progressive disease complicating the electrolyte profile, intrinsic tumor-related factors, variable risk factors that predispose towards development of ACS and concomitant use of multiple medications, which are associated with ACS.

Preventability:
Prompt treatment according to institutional guidelines is recommended in case of ACS. Correct patient selection to potentially exclude at-risk patients.

Impact on the risk-benefit balance of the product:
Overall, the frequency of ACS in the safety analysis population was uncommon: only 1 case has occurred in an adult patient with heavily pretreated, relapsed pancreatic cancer and baseline cerebellar abnormalities on magnetic resonance imaging (MRI) who was treated with selinexor 145 mg twice weekly (i.e., a very high dose which is no longer used); 2 cases occurred in pediatric patients with refractory AML, also with baseline cerebellar abnormalities and treated at very high doses no longer used.

Public health impact:
Considering the low number of suspected cases and the high doses were utilized in these cases which are no longer used anymore (indicated dosage is 80 mg BIW), minimal public health impact is expected from cases of ACS.

Important Potential Risk 2: Medication errors

Potential mechanisms:
An exact cause of typical Overdose during the clinical trial was not evaluated.

Evidence source(s) and strength of evidence:
Medication errors in the form of overdose were reported in 3 patients (0.3 %) in HM-Pool and 5 patients (0.9 %) in MM-Pool.

In HM-Pool (N = 996), TEAE of PT Overdose was reported in 3 (0.3 %) patients; all events were low grade (Grade 1 or Grade 2) and all events resolved. One Grade 2 event of Overdose

was associated with concurrently reported tumor lysis syndrome (Grade 3), hyponatraemia, nausea, hyperuricaemia, and fatigue and was reported in a patient that belongs to both HM-Pool and MM-Pool.

In MM-Pool (N = 552), TEAE of PT Overdose was reported in 5 (0.9 %) patients; all events were low grade (Grade 1 or Grade 2) and all events resolved. In addition to a patient with reported concurrent events mentioned above in HM-Pool, one patient with Grade 1 Overdose experienced concurrent Grade 3 thrombocytopenia and Grade 1 ALT increased, one patient with Grade 2 overdose had nausea, anorexia and Grade 4 thrombocytopenia and one patient with Grade 2 overdose had Grade 2 ALT increased.

Characterisation of the risk:
In HM-Pool (N = 996), TEAE of PT Overdose was reported in 3 (0.3 %) patients; all events were low grade (Grade 1 or Grade 2) and all events resolved. One Grade 2 event of Overdose was associated with concurrently reported tumor lysis syndrome (Grade 3), hyponatraemia, nausea, hyperuricaemia, and fatigue and was reported in a patient that belongs to both HM-Pool and MM-Pool.

In MM-Pool (N = 552), TEAE of PT Overdose was reported in 5 (0.9 %) patients; all events were low grade (Grade 1 or Grade 2) and all events resolved. In addition to a patient with reported concurrent events mentioned above in HM-Pool, one patient with Grade 1 Overdose experienced concurrent Grade 3 thrombocytopenia and Grade 1 ALT increased, one patient with Grade 2 overdose had nausea, anorexia and Grade 4 thrombocytopenia and one patient with Grade 2 overdose had Grade 2 ALT increased.

All patients in clinical trials with events associated with Overdose recovered. Out of 7 events reported overall (1 patient belonged to both Pools), 4 events led to dose reduction or interruption, none led to treatment discontinuation.

In summary, 3 and 5 events of ME Overdose were reported from HM-Pool and MM-Pool respectively. All events were low grade and resolved. Based on a review of available data, a clear causal association between selinexor and ME cannot be established.

Risk factors and risk groups:
Reported events of ME are confounded by age and concomitant use of several medications.

Preventability:
Patient compliance with the prescribed doing schedule.

Impact on the risk-benefit balance of the product:
Overall, the frequency of ME in the safety analysis population was uncommon: a total of 3 patients in the HM-Pool and 5 patients in the MM-Pool that corresponds to 0.3 % and 0.9 % of patients in each pool respectively experienced Overdose.

All TEAEs in both pools were Grade 1 or 2 in intensity. All TEAEs in both pools resolved.

Public health impact:
Considering the low number of serious AEs associated with ME and the fact that all patients recovered, minimal public health impact is expected from cases of ME.

SVII.3.2 Presentation of the missing information

Missing information: Use in patients with severe renal impairment

Evidence source:
Patients with estimated creatinine clearance of ≤ 20 mL/min were excluded from clinical trials in order to avoid confounding safety and efficacy results. In the HM-Pool, at study baseline 709 patients had normal renal function, 239 had mild / moderate impairment, and 28 had severe impairment, based on estimated creatinine clearance. In population PK analyses, the clearance values were similar in patients with mild, moderate, and severe renal impairment, indicating that no dose adjustment is necessary with advanced renal impairment. Because selinexor is not extensively cleared by renal excretion, severe renal impairment is not expected to have a clinically significant effect on the PK of selinexor. An AE analysis by baseline renal function did not suggest clear differences in the safety profiles of the subgroups by renal function.

Population in need of further characterisation:
As the safety and efficacy of selinexor have not been systematically studied in patients with severe renal impairment, these patients are included under missing information as a population in need of further characterization.

PART II: MODULE SVIII. SUMMARY OF THE SAFETY CONCERNS

Table SVIII - 1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Thrombocytopenia and Bleeding Severe infections due to Neutropenia
Important potential risks	Acute cerebellar syndrome Medication error
Missing information	Use in patients with severe renal impairment.

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. ROUTINE PHARMACOVIGILANCE ACTIVITIES
Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
Not applicable.

III.2. ADDITIONAL PHARMACOVIGILANCE ACTIVITIES
There are no additional PV activities ongoing or planned.

III.3. SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES
Not applicable.

PART IV. ART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES
There are no planned or ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1. ROUTINE RISK MINIMISATION MEASURES

Table Part V - 1: Description of routine risk minimisation measures by safety concern

<table>
<tr><th>Safety concern</th><th>Routine risk minimisation activities</th></tr>
<tr><td>Safety concern 1: Thrombo-cytopenia and Bleeding</td><td>
Routine risk communication: SmPC sections 4.2, 4.4, 4.8, PIL section 2 and 4
Routine risk minimisation activities recommending specific clinical measures to address the risk: PIL section 4
The following specific clinical measures are included in the SmPC Section 4.2

Dose modifications in the event of thrombocytopenia

Recommended selinexor dose modifications for adverse reactions are presented in Table 1 and Table 2.

Table 1 Prespecified dose modification steps for adverse reactions
<table>
<tr><th></th><th>Selinexor in combination with Bortezomib and Dexamethasone (SVd)</th><th>Selinexor in combinatior with Dexamethasone (Sd</th></tr>
<tr><td>Recommended starting dose</td><td>100 mg once weekly</td><td>80 mg Days 1 and 3 of eac week
(160 mg total per week)</td></tr>
<tr><td>First reduction</td><td>80 mg once weekly</td><td>100 mg once weekly</td></tr>
<tr><td>Second reduction</td><td>60 mg once weekly</td><td>80 mg once weekly</td></tr>
<tr><td>Third reduction</td><td>40 mg once weekly</td><td>60 mg once weekly</td></tr>
<tr><td colspan="3">Discontinue*</td></tr>
</table>
* If symptoms do not resolve, treatment should be discontinued

Table 2 Dose modification guidelines for adverse reactions
<table>
<tr><th>Adverse reaction[a]</th><th>Occurrence</th><th>Action</th></tr>
<tr><td colspan="3">Thrombocytopenia</td></tr>
<tr><td>Platelet count 25,000 to less than 75,000/mcL</td><td>Any</td><td>Reduce selinexor by 1 dose level (see Table 1).</td></tr>
<tr><td>Platelet count 25,000 to less than 75,000/mcL with concurrent bleeding</td><td>Any</td><td>Interrupt selinexor.
Restart selinexor at 1 dose level lower (see Table 1), after bleeding has resolved.</td></tr>
<tr><td>Platelet count less than 25,000/mcL</td><td>Any</td><td>Interrupt selinexor.
Monitor until platelet count returns to at least 50,000/mcL.</td></tr>
</table>
</td></tr>
</table>

	<table><tr><td></td><td></td><td>Restart selinexor at 1 dose level lower (see Table 1).</td></tr></table> In SmPC Section 4.4: • Patients should have their complete blood counts (CBC) assessed at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Thrombocytopenia • Thrombocytopenic events (thrombocytopenia and platelet count decreased) were frequently reported in patients receiving selinexor which can be severe (Grade 3/4). Grade 3/4 thrombocytopenia can sometimes lead to clinically significant bleeding and in rare cases may lead to potentially fatal haemorrhage (see section 4.8). Thrombocytopenia can be managed with dose interruptions, modifications, platelet transfusions, and / or other treatments as clinically indicated. Patients should be monitored for signs and symptoms of bleeding and evaluated promptly. For dose modification guidelines refer to Table 1 and Table 2 in section 4.2 of SmPC. In the PIL: NEXPOVIO may cause the following serious side effects: Very common (may affect more than 1 in 10 people) • reduced number of blood platelets Your doctor will carry out blood tests before you start taking NEXPOVIO, and as needed during and after treatment. These tests will be more frequent during the first two months of treatment to monitor your blood platelet counts. Your doctor may stop treatment or adjust the dose based on your platelet counts. Tell your doctor immediately if you have signs of reduced number of blood platelets such as: - easy or excessive bruising 40 - skin changes that appear as a rash of pinpoint-sized reddish-purple spots - prolonged bleeding from cuts - bleeding from your gums or nose - blood in your urine or stools Other routine risk minimisation measures beyond the Product Information: None Legal status: restricted medical prescription
Safety concern 2: Severe infections due to Neutropenia	Routine risk communication: SmPC sections 4.2, 4.4, 4.8, PIL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: The following specific clinical measures are included in the SmPC Section 4.2: **Dose Modifications in the event of neutropenia** For Grade 3 neutropenia without fever, reduce selinexor by one dose level below the current dose as shown in Table 1 (also in SmPC Section 4.2). For Grade 4 neutropenia or febrile neutropenia, withhold dose and institute supportive care measures until neutrophils return to Grade ≤ 2. Reinitiate selinexor at one dose level below the current dose as shown in Table 1. In SmPC Section 4.4: Neutropenia Neutropenia including severe neutropenia (Grade 3/4) has been reported with selinexor. In a few cases concurrent infections occurred in patients with Grade 3/4 neutropenia (see section 4.8). Patients with neutropenia should be monitored for signs of infection and evaluated promptly.

	Neutropenia can be managed with dose interruptions, modifications, and colony-stimulating factors as per medical guidelines. For dose modification guidelines refer to Table 1 and Table 2 in section 4.2. In the PIL: NEXPOVIO may cause the following serious side effects: Very common (may affect more than 1 in 10 people) • reduced number of red and white blood cells, including neutrophils and lymphocytes. Your doctor will carry out blood tests to monitor your red and white blood cell counts before you start taking NEXPOVIO and as needed during and after treatment. These tests will be more frequent during the first two months of treatment. Your doctor may stop treatment or adjust the dose based on your blood cell counts or may treat you with other medicines to increase cell counts. Tell your doctor immediately if you have signs of reduced neutrophils such as a fever Other routine risk minimisation measures beyond the Product Information: None Legal status: restricted medical prescription
Safety concern 3 Acute cerebellar syndrome	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None Legal status: restricted medical prescription
Safety concern 4: Medication errors	Routine risk communication: Labelling, SmPC section 4.9. Routine risk minimisation activities recommending specific clinical measures to address the risk: The following specific clinical measures are included in the labelling and SmPC section 4.9: • In general, overdoses have been associated with similar side effects to those reported for standard dosing and have generally been reversible within 1 week. Symptoms Potential acute symptoms include nausea, vomiting, diarrhoea, dehydration and confusion. Potential signs include low sodium levels, elevated liver enzymes, and low blood counts. Patients should be monitored closely and provided with supportive care as appropriate. No fatalities due to overdose have been reported to date. Management In the event of an overdose, monitor the patient for any adverse reactions and appropriate symptomatic treatment should be provided immediately. Other routine risk minimisation measures beyond the Product Information: None Legal status: restricted medical prescription
Safety concern 5: Use in patients with severe renal impairment	Routine risk communication: SmPC section 5.2 Routine risk minimisation activities recommending specific clinical measures to address the risk: The following specific clinical measures are included in the SmPC: • Section 4.2: Renal impairment No dose adjustment of selinexor is required for patients with mild, moderate, or severe renal impairment (see section 5.2). There are no data in patients with end-stage renal disease or haemodialysis to support a dose recommendation. • Section 5.2:

	The degree of renal impairment was determined by creatinine clearance as estimated by the Cockcroft-Gault equation. Results from population PK analyses of patients with normal (n = 283,CLcr:> 90mL/min), mild (n = 309,CLcr:60 to89ml/min), moderate (n = 185,CLcr:30to59ml/min) or severe (n = 13,Clcr;15to29ml/min) renal dysfunction indicated that creatinine clearance had no impact on the PK of NEXPOVIO. 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 Other routine risk minimisation measures beyond the Product Information: None Legal status: restricted medical prescription

V.2. ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. SUMMARY OF RISK MINIMISATION MEASURES

Table Part V - 3: 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 Legal status: restricted medical prescription Additional risk minimization measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none
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 Legal status: restricted medical prescription Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none
Safety concern 3: Acute cerebellar syndrome	Routine risk minimisation measures:. Legal status: restricted medical prescription Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none
Safety concern 4: Medication error	Routine risk communication measure: Labelling and SmPC section 4.9 Legal status: restricted medical prescription Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none
Safety concern 5: Use in patients with severe renal impairment	Routine risk minimisation measures: SmPC section 5.2 where information on the missing information is provided. Legal status: restricted medical prescription Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR NEXPOVIO (SELINEXOR)

This is a summary of the risk management plan (RMP) for NEXPOVIO. The RMP details important risks of NEXPOVIO, how these risks can be minimised, and how more information will be obtained about NEXPOVIO 's risks and uncertainties (missing information).

NEXPOVIO 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how NEXPOVIO should be used.

This summary of the RMP for NEXPOVIO should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR). Important new concerns or changes to the current ones will be included in updates of NEXPOVIO 's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

NEXPOVIO is authorised 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 (see SmPC for the full indication). NEXPOVIO is indicated in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy (see SmPC for the full indication). It contains selinexor as the active substance and it is given by oral route.

Further information about the evaluation of NEXPOVIO’s benefits can be found in NEXPOVIO’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage
https://www.ema.europa.eu/en/medicines/human/EPAR/nexpovio

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of NEXPOVIO, together with measures to minimise such risks and the proposed studies for learning more about NEXPOVIO 's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR (Periodic Safety Update Report) assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities.*

If important information that may affect the safe use of NEXPOVIO which is not yet available, it is listed under 'missing information' below.

II.A. List of important risks and missing information

Important risks of NEXPOVIO are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of NEXPOVIO. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Thrombocytopenia and Bleeding Severe infections due to Neutropenia
Important potential risks	Acute cerebellar syndrome Medication error
Missing information	Use in patients with severe renal impairment

II.B. Summary of important risks

Important identified risk: Thrombocytopenia and Bleeding	
Evidence for linking the risk to the medicine	Thrombocytopenia was experienced frequently by patients in the target population in clinical trials. Almost half of the patients with events in completed trials had thrombocytopenia of Grade ≥ 3 intensity and one patient died from bleeding due to thrombocytopenia considered possibly related to selinexor treatment.
Risk factors and risk groups	Assessment of the contribution of selinexor to the development of thrombocytopenia in the patients under study was influenced by multiple confounding variables including baseline thrombocytopenia, bone marrow cellularity and replacement with malignant plasma cells, disease indication, patient age, previous treatments, advanced disease, current comorbidities, concomitant medications and the complexity of the patient populations studied.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.8, PIL sections 2 and 4 Legal status: restricted medical prescription Additional risk minimisation measures: none
Important identified risk: Severe infections due to Neutropenia	

Evidence for linking the risk to the medicine	Adverse events of neutropenia were experienced frequently by patients in the target population in clinical trials. About 30 % of the patients had neutropenia at some point of treatment and most instances were Grade 3 events. Neutropenia considered related to selinexor treatment was reported for about a quarter of the patients. About 15 % of patients with neutropenia had ≥ grade 3 infections related events.
Risk factors and risk groups	Main risk factors for the development of neutropenia in cancer patients are age, poor performance status, advanced disease, certain comorbidities (renal impairment, hepatic impairment, cardiovascular disease), low baseline blood cell counts, low body surface area / body mass index, treatment with myelosuppressive chemotherapies, and specific genetic polymorphisms. Neutropenia can increase the risk of infections in these heavily pre-treated patients with underlying hematological malignancy. Infections are common in patients with advanced hematological malignancies due to the underlying cytopenia secondary to malignancy, various anti-neoplastic treatments, advanced age and associated co-morbidities.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8, PIL sections 2 and 4 Legal status: restricted medical prescription Additional risk minimisation measures: none
Important potential risk: Acute cerebellar syndrome	
Evidence for linking the risk to the medicine	Three cases of ACS related events were reported in Selinexor development program in > 3111 patients treated of March 31, 2019. One (1) case has occurred in an adult patient with heavily pretreated, relapsed pancreatic cancer and baseline cerebellar abnormalities on magnetic resonance imaging (MRI) who was treated with selinexor 145 mg twice weekly (i.e., a very high dose which is no longer used); 2 cases occurred in pediatric patients with refractory AML, also with baseline cerebellar abnormalities. and treated at very high doses no longer used. No new reports were identified since these cases. were reported and further study of higher doses was discontinued. No cases of ACS have occurred in adult patients with MM or other hematologic malignancies. Because ACS can be associated with significant morbidity and there are direct implications for monitoring and management, ACS has been characterized as an important potential risk of selinexor.

Risk factors and risk groups	Reported events of ACS are often confounded by a variety of factors including central nervous system disorders due to progressive disease complicating the electrolyte profile, intrinsic tumor-related factors, variable risk factors that predispose towards development of ACS and concomitant use of multiple medications, which are associated with ACS.
Risk minimisation measures	Routine risk minimisation measures: Legal status: restricted medical prescription Additional risk minimisation measures: none

Important potential risk: Medication errors	
Evidence for linking the risk to the medicine	Medication errors (ME) overdose were reported in 3 and 5 patients in HM-Pool and MM-Pool respectively. All events were low grade and resolved. A clear causal association cannot be established, ME has been recognized as an important potential risk of selinexor.
Risk factors and risk groups	Reported events of ME are confounded by age and concomitant use of several medications.
Risk minimisation measures	Routine risk minimization measures: Labelling, SmPC 4.9 Legal status: restricted medical prescription Additional risk minimization measures: none

Missing information: Use in patients with severe renal impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 5.2 where information on the missing information are provided. Legal status: restricted medical prescription Additional risk minimisation measures: none

II.C. Post-authorisation development plan

II.C.1. Studies which are conditions of the marketing authorization
There are no studies which are conditions of the marketing authorisation or specific obligation of NEXPOVIO.

II.C.2. Other studies in post-authorisation development plan
There are no additional PV activities ongoing or planned.

PART VII. ANNEXES

Annex 1 –Not Applicable
Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme (not applicable)
Annex 3- Protocols for proposed, on-going and completed studies in the pharmacovigilance plan (not applicable)
Annex 4 - Specific adverse drug reaction follow-up forms (not applicable)
Annex 5 - Protocols for proposed and on-going studies in RMP part IV (not applicable) *Annex 6* - Details of proposed additional risk minimisation activities (not applicable)
Annex 7 - Other supporting data (including referenced material)
Annex 8 - Summary of changes to the risk management plan over time.

Annex 1 - EudraVigilance Interface

Not applicable

Annex 2 - Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Table 1 Annex II: Planned and on-going studies

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones
None			

Table 2 Annex II: Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission
KCP-330-023	**Primary** •No primary safety objective **Secondary** • To compare the incidence of any Grade ≥ 2 peripheral neuropathy in patients randomized to the SVd Arm versus patients randomized to the Vd Arm • To assess the safety and tolerability of treatment with SVd versus Vd in patients with RRMM • To compare patient-reported peripheral neuropathy as measured by the European Organization for Research and Treatment of Cancer (EORTC) Chemotherapy-induced Peripheral Neuropathy (QLQ-CIPN20) instrument in patients randomized to the SVd Arm versus the Vd Arm	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	Pending

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan.

Table of Contents

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP.
Not applicable.

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP.
Not applicable.

Part C: Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority.
Not applicable

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities

Not applicable.

Annex 7 - Other supporting data (including referenced material)

Bishton MJ, Harrison SJ, Martin BP, McLaughlin N, James C, Joselsson EC, et al. Deciphering the molecular and biologic processes that mediate histone deacetylase inhibitor-induced thrombocytopenia. Blood 2011;117:3658-68.

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Cure Research 2003, http://www.cureresearch.com/m/multiple_myeloma/stats-country_printer.htm, accessed Dec 2018.

Cancer Research UK, https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence#ref-4, accessed Sep 2018.

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Annex 8 - Summary of changes to the risk management plan over time.

Version	Approval date Procedure	Change
0.1	Not applicable < procedure number>	Initial RMP draft
0.2	25 November2019	Reclassification of important risks to non-important risks, including anaemia, nausea, vomiting, diarrhoea, dizziness, impact on male fertility and use in pregnant or breastfeeding in women. Infection due to neutropenia were considered as important identified risk. Medication error were considered as important potential risk.
0.3	Not yet approved – updated draft of RMP < procedure number>	To address CHMP request (Comment 9 in the 2nd LoOI) to add the BOSTON/ KCP-330-023 study as additional pharmacovigilance activity (cat 3 PASS) to further characterize the safety concerns of selinexor.
0.4	Not yet approved – updated draft of RMP	To add the commitment to submit the KCP-330-023/ BOSTON study CSR within 2 months after positive opinion.
1.0	Approved (CHMP positive opinion dated 28 January 2021) EMEA/H/C/005127/0000	Updated product indication, KCP-330-023/ BOSTON study moved from Part III to Part IV including final wording on the specific obligation as requested on 26Jan2021 by EMA, The final wording is in line with the wording in ANNEX II of the PI
1.1	Not yet approved	Completion of KCP-330-023 study to fulfill the specific obligation. Update in the safety data to reflect the safety information captured during the KCP-330-023 study and update in the exposure data. Proposed additional product indication and dosing regimen. Revisions to align with the RMP template and to be consistent with PI.
2.0	Approved (CHMP positive opinion dated 19 May 2022) EMEA/H/C/005127/II/0001/G	Per PRAC guidance cataract has been reverted to non-important risk as it is considered that cataract is not likely to have an impact on the risk-benefit balance and no additional risk minimizations measures are warranted.
3.0	Approved (	Per PRAC recommendation (EMEA/H/C/PSUSA/00010926/202209), Fatigue, Decreased Appetite, Weight Decreased, Hyponatraemia, Confusional state have been removed as important identified risks as they have been sufficiently characterised and are managed through appropriate labelling. These risks will continue to be monitored through routine pharmacovigilance.

		Additionally, Tumor lysis syndrome has been removed as an important potential risk, as per PRAC recommendation (EMEA/H/C/PSUSA/00010926/202209), as this risk is considered to be well characterized and addressed in the SmPC sections 4.4 and 4.8 Part I- MAH was transferred from Karyopharm to Stemline Part II: Module SIII – Clinical trial exposure (Table SIII - 1 to Table SIII - 4) were updated with exposure as of 25 September 2022. Part II: Module SV was updated with post-authorisation exposure in the US as of 25 September 2022. Other minor administrative changes were made throughout the document.
4.0	Not yet approved	Update to remove “use in patients with severe hepatic impairment” from the list of missing information in the RMP based on the study results from KCP-330-027. The following sections are updated accordingly: • Part II SIV.1 – Update to exclusion criteria of non-adequate hepatic function, • SIV.3 (Table SIV - 3) – Update to exposure special populations of patients with relevant comorbidities, • Update to remove missing information (Use in patients with severe hepatic impairment) from SVII.1.2, from list of safety concerns and reasons for removal [SVII.2], from presentation of missing information [SVII 3.2], from summary of safety concerns [SVIII (Table SVIII - 1)], • Update to remove safety concern, “Use in patients with severe hepatic impairment” from Routine Risk Minimization Measures [PART V.1 (Table Part V - 1)], Summary of risk minimization measures [PART V.3 (Table Part V - 3)], List of important risks and missing information [PART VI, II.A], and Summary of important risks [PART VI, II.B] • Part II: Module SIII – Clinical trial exposure (Table SIII - 1 to Table SIII - 4) and Module SV.1.2 were updated with exposure as of 25 March 2025.