CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212306Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	Original 505(b)(1)
Application Number(s)	NDA 212306
Priority or Standard	Priority
Submit Date(s)	August 5, 2018
Received Date(s)	August 6, 2018
PDUFA Goal Date	April 6, 2019 (Extended to July 6, 2019)
Division/Office	DHP/OHOP
Review Completion Date	July 1, 2019
Established Name	Selinexor
(Proposed) Trade Name	XPOVIO®
Pharmacologic Class	Nuclear export inhibitor
Code name	
Applicant	Karyopharm Therapeutics
Formulation(s)	Tablet, 20 mg, immediate-release
Dosing Regimen	80 mg twice weekly
Applicant Proposed Indication(s)/Population(s)	XPOVIO is indicated in combination with dexamethasone, for the treatment of patients with relapsed refractory multiple myeloma who have received at least three prior therapies and whose disease is refractory to at least one proteasome inhibitor, at least one immunomodulatory agent, and an anti-CD38 monoclonal antibody.
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	XPOVIO is indicated in combination with dexamethasone, for the treatment of patients with relapsed refractory multiple myeloma 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 antibody.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AUC	area under the concentration time curve
ADaM	Analysis Dataset Model
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
APC	adenomatous polyposis coli
ASCT	autologous stem cell transplantation
AUC	area under the curve
BCL-2	B-cell lymphoma 2
BCL-6	B-cell lymphoma 6
BCLPD	bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab
BCLPD-R	BCLPD-refractory
BIW	twice weekly
BLA	Biologics License Application
bpm	beats per minute
BSC	best supportive care
BUN	blood urea nitrogen
CBR	clinical benefit rate
CD38	cluster of differentiation 38
CDER	Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximal/peak plasma concentration
CMC	Chemistry, Manufacturing, and Controls
CML	chronic myelogenous leukemia
CNS	central nervous system
COA	clinical outcome assessment
CR	complete response
CRF	case report form
CRM	chromosome region maintenance 1 protein
CSR	clinical study report
CTCL	cutaneous T-cell lymphoma
Cys	cysteine

DBP	diastolic blood pressure
DCR	disease control rate
DDI	drug-drug interactions
DEPI	Division of Epidemiology
Dex	dexamethasone
DHOT	Division of Hematology Oncology Toxicology
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DMEPA	Division of Medication Error and Prevention Analysis
DMF	Drug Master File
DOR	duration of exposure
DRISK	Division of Risk Management
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
EDR	electronic document room
EFD	embryo-fetal development
EHR	electronic health record
EOP1	end of phase 1
FACT-MM	Function Assessment of Cancer Therapy – Multiple Myeloma
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FD&C Act	Federal Food, Drug, and Cosmetic Act
FHAD	Flatiron Health Analytics Database
FISH	fluorescence in-situ hybridization
FLC	free light chain
FOXO	foxhead box O
GCP	good clinical practice
G-SCF	granulocyte colony stimulating factor
GD	gestation day
GFP	green fluorescent protein
GLP	good laboratory practice
GMR	geometric mean ratio
GRP	growth regulatory protein
hERG	human Ether-à-go-go-Related Gene
HMA	hypomethylating agent
HR	hazard ratio or heart rate
HR-QoL	Health-related Quality of Life
5-HT3	5-hydroxytryptamine
IC50	half maximal inhibitory concentration

ICH	International Conference on Harmonization
IkB	inhibitor of kappa B
IMiD	immunomodulatory drug/agent
IMWG	International Myeloma Working Group
IND	Investigational New Drug
IPTW	inverse probability of treatment weight
IR	information request
IRC	Independent Review Committee
IRT	Interdisciplinary Review Team
ISE	Integrated Summary of Effectiveness
ISS	Integrated Summary of Safety or International Staging System
ITT	intent-to-treat
IV	intravenous
KPT-330	selinexor
LDAC	low-dose Ara-C
mAb	monoclonal antibody
MAO-B	monoamine oxidase-B
Mdm2	mouse double minute 2 homolog
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MM	multiple myeloma
MNPCE	micronucleated polychromatic erythrocytes
MR	minimal response
MTD	maximum tolerated dose
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NA	not applicable
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New Drug Application
NDMM	newly diagnosed multiple myeloma
NE	not estimable/evaluable
NES	nuclear export signal
NHL	non-Hodgkin's lymphoma
NME	new molecular entity
NOD-SCID	non-obese diabetic-severe combined immunodeficient
OB	Office of Biotechnology
OCP	Office of Clinical Pharmacology
OCS	Office of Computational Science
ODAC	Oncology Drug Advisory Committee
ODC	ornithine decarboxylase
OPDP	Office of Prescription Drug Promotion

OPQ	Office of Pharmaceutical Quality
ORR	overall response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
PD	pharmacodynamics
PFS	progression free survival
PI	proteasome inhibitor
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP2Aα	protein phosphate 2Aα
PR	partial response
pRb	phosphorylated retinoblastoma protein
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PS	propensity score
PTCL	peripheral T-cell lymphoma
PTEN	phosphatase and tensin homolog
QoL	quality of life
REMS	risk evaluation and mitigation strategy
RNA	ribonucleic acid
RCT	randomized controlled trial
RP2D	recommended phase 2 dose
RRMM	relapsed/refractory multiple myeloma
RT	Richter's transformation
RWD	real-world data
S9	S9 fraction of liver microsomes
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SBP	systolic blood pressure
sCR	stringent complete response
SD	standard deviation or stable disease
SDTM	Study Data Tabulation Model
sFLC	serum free light chains
SPEP	serum protein electrophoresis
TEAE	treatment emergent adverse event
TK	toxicokinetics
T_{max}	time to maximal/peak plasma concentration

TOI	trial outcomes index
TSP	tumor suppressor protein
TTP	time to progression
ULN	upper limit of normal
USP	United States Pharmacopeia
USPI	U.S. prescribing information
VGPR	very good partial response
WBC	white blood cell count
WM	Waldenström's macroglobulinemia
WRO	written responses only
XPO1	exportin 1

1 Executive Summary

1.1 Product Introduction

Selinexor (XPOVIO®) is a new molecular entity. NDA 212306 was originally submitted for the proposed indication of selinexor, an oral XPO1 inhibitor, in combination with dexamethasone, for the treatment of patients with relapsed refractory multiple myeloma (RRMM) who have received at least three prior therapies and whose disease is refractory to at least one proteasome inhibitor, at least one immunomodulatory agent, and an anti-CD38 monoclonal antibody. The revised indication is for the treatment of patients with relapsed refractory multiple myeloma 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 antibody.

Selinexor is a first-in-class, oral, small molecule inhibitor of the nuclear export protein, exportin 1 (XPO1). Inhibition of XPO1 is hypothesized to restore normal tumor suppressor pathways and lead to selective apoptosis of neoplastic cells.

The proposed dose is selinexor 80 mg orally twice weekly in combination with dexamethasone 20 mg twice weekly on Days 1 and 3 for Weeks 1 through 4 of each 28-day cycle, until disease progression or unacceptable toxicity.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The review team recommends accelerated approval for selinexor for the indication "in combination with dexamethasone for the treatment of adult patients with relapsed refractory multiple myeloma (RRMM) who have received at least four prior therapies and whose disease is refractory or intolerant to at least two prior proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody." The recommendation is based on the overall response rates (ORR) observed in Part 2 of the single-arm trial, KCP-330-012 (STORM), and supported by additional information from the ongoing phase 3, randomized, trial, KCP-330-023 (BOSTON).

The approval recommendation for selinexor is for accelerated approval. Additional information from confirmatory trials is needed to verify the benefit of selinexor in patients with multiple myeloma. The ongoing BOSTON trial of selinexor in combination with bortezomib and dexamethasone compared to bortezomib and dexamethasone alone will serve as the confirmatory trial and was issued as a post-marketing requirement (PMR). Other PMRs include the conduct of a randomized phase 2 trial to characterize the safety and efficacy of at least 2 doses of selinexor, conduct of a hepatic impairment trial, and conduct of a dedicated drug interaction trial.

The STORM trial was a multicenter, open-label, single arm trial evaluating selinexor in combination with dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM). Part 2 of the trial enrolled 123 patients with RRMM who had received at least three prior lines of therapy including an alkylating agent, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, and a glucocorticoid, and whose disease was considered refractory to at least one proteasome inhibitor (i.e., bortezomib and/or carfilzomib), at least one immunomodulatory agent (i.e., lenalidomide and/or pomalidomide), and an anti-CD38 monoclonal antibody (i.e., daratumumab).

The primary endpoint was ORR, according to IMWG criteria. The modified ITT (mITT) population in Part 2 included 122 patients with triple-class refractory MM who met all eligibility criteria and received at least one dose of selinexor and dexamethasone. The ORR was 25.4% (95% CI: 18%, 34.1%), and the median DOR was 4.4 months (range 0.8 to 9.0 months). Responses included 2 patients with sCR, 6 patients with VGPR, and 23 patients with PR.

The FDA identified several deficiencies with the trial design, as it relates to effectiveness, which include the following:

- The STORM trial was a single arm trial evaluating the combination of selinexor and dexamethasone. This trial design did not allow for the isolation of effect of selinexor. Of note, there were no responses in the phase 1 trial when selinexor was evaluated as monotherapy.
- There was uncertainty regarding the selected dose. Lower doses of selinexor in combination with dexamethasone were not evaluated in the phase 1 trial.

The application was presented at an Oncology Drug Advisory Committee (ODAC) Meeting. The ODAC committee members voted in favor of delaying approval until results of the randomized phase 3 BOSTON trial are available. After the ODAC meeting and discussion with the Agency, the Applicant submitted a major amendment which included response data from the ongoing phase 3, randomized, trial, KCP-330-023 (BOSTON). Based on this additional information, the review team recommended accelerated approval for selinexor in a more refractory patient population than that initially proposed by the Applicant. This refractory patient population represents a population for which there is no approved therapy and those who have for all intents and purposes exhausted available therapy. The efficacy results for this more refractory patient population (presented later in the review), along with the additional information from BOSTON, support the determination that there is substantial evidence of effectiveness for selinexor in patients with 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 antibody.

1.3 Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The evidence of effectiveness of selinexor in combination with dexamethasone in patients with 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 antibody is supported by the subgroup overall response rate (ORR) observed in the STORM trial of 25.3% with a median duration of response (mDOR) of 3.8 months. Selinexor is associated with significant toxicity which results in a questionable benefit-risk profile. Specifically, in Part 2 of STORM, all patients (100%) experienced at least one treatment-emergent adverse event (TEAE), nearly two-thirds (60.2%) of patients experienced a serious adverse event (SAE), most patients (91.1%) required a dose modification due to a TEAE and over one-quarter (26.8%) of patients discontinued treatment with selinexor-dexamethasone due to a TEAE. After the ODAC meeting and discussion with the Agency, the Applicant submitted a major amendment which included response data from the ongoing phase 3, randomized trial, KCP-330-023 (BOSTON). Based on this additional information, the review team recommended accelerated approval for selinexor in a more refractory patient population than initially proposed by the Applicant. This refractory patient population represents a population for which there is no approved therapy and those who have for all intents and purposes exhausted available therapy. In this patient population that has exhausted available therapy, the risk-benefit profile of selinexor is acceptable. The prescribing information will include warnings and precautions for thrombocytopenia, neutropenia, gastrointestinal toxicity, anorexia/weight loss, hyponatremia, infections, neurological toxicities, and embryo-fetal toxicity to inform prescribers of the risks associated with selinexor administration. The prescribing information will also include dose modification guidelines and concomitant medication recommendations to allow for the safe administration of selinexor. Post-marketing requirements were issued for a confirmatory clinical trial to verify the benefit of selinexor in patients with multiple myeloma, a randomized phase 2 trial to characterize the safety and efficacy of lower doses of selinexor, a hepatic impairment trial, and a dedicated drug interaction trial.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Multiple myeloma is an incurable hematologic malignancy.	Given the incurable nature of the disease, there is an unmet medical need for new anti-myeloma therapies.
Current Treatment Options	There are multiple treatment options available for RRMM which include: bortezomib, lenalidomide, pomalidomide, carfilzomib, elotuzumab, ixazomib, daratumumab, and panobinostat.	The revised patient population is one that has received at least four prior lines of therapy, and is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 antibody.
Benefit	ORR 25.3% with median DOR 3.8 months in the subgroup.	The ORR of 25% is acceptable in this refractory patient population.
Risk and Risk Management	• TEAEs occurred in 100% of patients, 60.2% of patients experienced an SAE, 91.1% required a dose modification due to a TEAE, and 26.8% of patients discontinued treatment with selinexor-dexamethasone due to a TEAE. • There is uncertainty regarding the appropriate dose of selinexor in combination in dexamethasone in this patient population. Lower doses of selinexor in combination with dexamethasone were not studied in the phase 1 trial and a clear dose-exposure relationship for safety was observed.	The prescribing information will include warnings and precautions for thrombocytopenia, neutropenia, gastrointestinal toxicity, anorexia/weight loss, hyponatremia, infections, neurological toxicities, and embryo-fetal toxicity, to inform prescribers of the risks associated with selinexor administration.

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☑	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	☑	Clinical outcome assessment (COA) data, such as			
			☑	Patient reported outcome (PRO)	Section 7.2.1 KCP-330-012 (STORM) – Study Endpoints Section 7.2.2 Efficacy Results – Secondary or exploratory COA (PRO) endpoints
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

_____
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1 Analysis of Condition

Multiple myeloma (MM) is a hematologic malignancy characterized by clonal expansion of plasma cells in the bone marrow and over-production of monoclonal immunoglobulins. The clinical features resulting from the accumulation of plasma cells or excess free light chains include hypercalcemia, renal dysfunction, anemia, bone pain and pathologic fractures, and impaired immunity.

MM is the second most common hematologic malignancy, accounting for nearly 2% of all new cancer cases and deaths. There will be approximately 32,110 new cases of MM and 12,960 deaths from MM in the U.S. in 2019 (American Cancer Society, Key Statistics About Multiple Myeloma). MM affects more men than women, with an incidence of 8.2 males to 5.4 females affected per 100,000 between 2011 and 2015. MM also disproportionately affects blacks with an incidence of 13.4 cases in blacks compared to 5.8 cases per 100,000 in non-Hispanic whites between 2011 and 2015. MM primarily affects older individuals, with a median age at diagnosis of 69 years (National Cancer Institute Cancer Stat Facts: Multiple Myeloma).

Significant advances have been made in the treatment of MM in recent decades with the use of high-dose therapy in combination with autologous stem cell transplantation (ASCT), and the introduction of new classes of therapeutic agents, including proteasome inhibitors (PIs), immunomodulatory agents (IMiDs), and monoclonal antibodies (mAb). In newly diagnosed patients who are eligible for ASCT, 4-year survival rates are over 80% for patients with standard-risk disease, and nearly 70% for patients with high-risk disease (Paquin, 2018). However, despite recent advances, MM is not considered curable. Most patients will eventually relapse and are likely to develop refractory disease. Patients who become refractory to the major classes of available anti-myeloma therapies have very poor outcomes (Kumar, 2017; Gandhi, 2018). Therefore, there is an urgent need for new therapies for patients with relapsed/refractory MM (RRMM) who have exhausted available therapies.

2.2 Analysis of Current Treatment Options

Current FDA-approved agents for the treatment of MM are listed in Table 1. Standard of care treatment for newly-diagnosed MM (NDMM) typically consists of doublet- or triplet-drug regimens. In patients deemed eligible for ASCT, induction chemotherapy is followed by ASCT and maintenance therapy. Nine drugs are specifically approved for the treatment of RRMM. Bortezomib is also approved for the retreatment of patients with RRMM who previously had at least a partial response to a bortezomib-containing regimen, and recent studies suggest that patients with RRMM may also respond to retreatment with agents they were previously

refractory to when these agents are incorporated into novel combination regimens (Nooka, 2016; Lakshman, 2017; Hussain, 2018).

Table 1: Currently Available Therapies for the Treatment of RRMM

Drug	Approval	Indication	Endpoint	Trial Design/Results
Velcade (bortezomib)	Accelerated (2003)	MM, at least 2 prior lines	ORR	Single-arm trial: ORR 28%
Velcade (bortezomib)	Regular (2005)	MM, 1-3 prior lines	TTP/OS	RCT: V vs. dex TTP: 6.2 months vs. 3.5 months (HR=0.55) OS: HR=0.57
Doxil Liposomal (doxorubicin HCl)	Regular (2007)	MM, at least 1 prior line	TTP	RCT: Doxil + V vs. V TTP: 9.3 vs. 6.5 months (HR=0.55)
Revlimid (lenalidomide) with dex	Regular (2005)	MM, at least 1 prior line	TTP	RCT: Rd vs. dex Study 1: TTP: 13.9 vs. 4.7 months (HR=0.285) Study 2: TTP: 12.1 vs. 4.7 months (HR=0.324)
Kyprolis (carfilzomib)	Accelerated (2012)	MM, at least 1 prior line	ORR	Single-arm trial: ORR 23%
Kyprolis with Rd	Regular (2015)	MM, 1-3 prior lines	PFS	RCT: KRd vs. Rd PFS: 26.3 vs. 17.6 months (HR= 0.69)
Kyprolis with dex	Regular (2016)	MM, 1-3 prior lines	PFS	RCT: Kd vs. Vd PFS: 18.7 vs. 9.4 months
Pomalyst (pomalidomide)	Accelerated (2013)	MM, at least 2 prior lines, including len and bortez	ORR	RCT: P vs Pd ORR: 7.4% vs. 29.2%
Pomalyst (pomalidomide) with dex	Regular (2015)	MM, at least 2 prior lines, including len and PI	PFS/OS	RCT: Pd vs. dex PFS: 3.6 vs. 1.8 months (HR=0.45) OS: 12.4 vs. 8.0 months (HR=0.70)
Farydak (panobinostat) with Vd	Accelerated (2015)	MM, at least 2 prior lines, including bortez and IMiD	PFS	RCT: PVd vs. Vd PFS: 10.6 vs. 5.8 months (HR=0.52)

Ninlaro (ixazomib) with Rd	Regular (2015)	MM, at least 1 prior line	PFS	RCT: Ixaz + Rd vs. placebo + Rd PFS: 20.6 vs. 14.7 months
Darzalex (daratumumab)	Accelerated (2015)	MM, at least 3 prior lines, including PI and IMiD	ORR	Single-arm trial ORR: 29% (median 5 prior lines of therapy)
Darzalex with Rd	Regular (2016)	MM, at least 1 prior line	PFS	RCT: DRd vs. Rd PFS: NE vs. 18.4 months (HR=0.37) ORR: 91.3%
Darzalex with Vd	Regular (2016)	MM, at least 1 prior line	PFS	RCT: DVd vs. Vd PFS: NE vs. 7.2 months (HR=0.39) ORR: 79.3% (median 2 prior lines of therapy)
Darzalex with Pd	Regular (2017)	MM, at least 2 prior lines, including len and PI	ORR	Single-arm trial ORR: 59.2% (median 4 prior lines of therapy)
Empliciti (elotuzumab) with Rd	Regular (2015)	MM, 1-3 prior lines	PFS	RCT: ERd vs. Rd PFS: 19.4 vs. 14.9 months (HR=0.70)
Empliciti (elotuzumab) with Pd	Regular (2018)	MM, at least 2 prior lines, including len and PI	PFS	RCT: EPd vs. Pd PFS: 10.3 vs. 4.7 months (HR= 0.54)

Abbreviations: MM = multiple myeloma; ORR = overall response rate; TTP = time to progression; OS = overall survival; RCT = randomized controlled trial; V = Velcade; dex = dexamethasone; HR = hazard ratio; Rd = Revlimid + dex; PFS = progression-free survival; KRd = Kyprolis + Rd; Kd = Kyprolis + dex; Vd = Velcade + dex; len = lenalidomide; PI = proteasome inhibitor; P = pomalidomide; Pd = pomalidomide + dex; PVd = panobinostat + Vd; Ixaz = ixazomib; IMiD = immunomodulatory agent; DRd = daratumumab + Rd; NE = not estimable; DVd = daratumumab + Vd; ERd = elotuzumab + Rd; EPd = Elotuzumab + Pd
(Source: FDA)

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

Selinexor is a new molecular entity and is not currently marketed.

3.2 Summary of Pre-submission/Submission Regulatory Activity

The trials included in this application were conducted under IND 114042, which was opened in the U.S. on June 8, 2012.

The key U.S. regulatory activities are listed in Table 2.

Table 2: Key U.S. Pre-submission and Post-submission Regulatory Activities

Date	Regulatory Activity	Details
January 5, 2015	Orphan Designation	14-4590
November 24, 2014	Type B (EOP1) Meeting	Discussed initial design (Part 1) of KCP-330-012
August 26, 2016	Type C Meeting	Discussed dose expansion (Part 2) of KCP-330-012
March 3, 2017	Partial Clinical Hold	IND 114042 placed on partial clinical hold
March 27, 2017	Removal of Partial Clinical Hold	Removal of partial clinical hold on IND 11042 after review of Sponsor's complete response
September 28, 2017	Type C Meeting (WRO)	Embryo-fetal toxicity in second species not needed
January 31, 2018	Type C Meeting	Discussed plans for KCP-330-012 SAP, ISS, and ISE to support indication in penta-refractory MM
April 2, 2018	Fast Track Designation	Granted
May 11, 2018	Type C Meeting (WRO)	CMC update
May 15, 2018	Type C Meeting (WRO)	Animal carcinogenicity studies not needed
June 22, 2018	Pre-NDA Meeting	Discuss contents/organization of proposed NDA

July 17, 2018	Rolling Review	Granted
June 29, 2018	NDA Submission Part 1	2.3, 2.4, 2.6, 3, 4, and related Module 1 documents
August 4, 2018	NDA Submission Part 2	2.5, 2.7, 5, and related Module 1 documents
February 26, 2019	Oncologic Drugs Advisory Committee (ODAC) Meeting	ODAC voted in favor of delaying consideration of approval until results of the randomized Phase 3 BOSTON trial are available
March 11, 2019	Meeting	Post-ODAC discussion
March 13, 2019	Major Amendment	Extension of PDUFA action date by 90 days to July 6, 2019

Abbreviations: EOP1 = end of phase 1; IND = investigational new drug; WRO = written response only; SAP = statistical analysis plan; ISS = integrated summary of safety; ISE = integrated summary of effectiveness; CMC = chemistry, manufacturing, and controls; NDA = new drug application; ODAC = Oncologic Drugs Advisory Committee; PDUFA = Prescription Drug User Fee Act
(Source: FDA)

The FDA placed IND 114042 on a partial clinical hold on March 3, 2017 after the Sponsor identified serious adverse events (SAEs) in both company-sponsored and investigator-sponsored clinical trials that were not captured in their safety database. FDA determined that this issue presented unreasonable and significant risk of illness or injury to human subjects and that there was insufficient information to assess risks to human subjects (21 CFR 312.42(b)(2)(i)). In addition, FDA determined that the Investigator Brochure, version 6.0, did not contain a list of cumulative SAEs, and therefore was misleading, erroneous, or materially incomplete (21 CFR 312.42(b)(2)(i)). The partial clinical hold was removed on March 27, 2017.

The Applicant included a statement in the NDA submission that "In connection with the partial clinical hold instituted by the Division on 03 March 2017 and removal of the hold on 27 March 2017, Karyopharm corrected the deficiencies described in the hold and established or improved company-wide processes to ensure continued compliance with respect to the timely and complete reporting of all safety information. For data included in the New Drug Application (NDA) 212306, additional measures were taken to confirm the integrity and accuracy of all selinexor data, including safety data, and we believe all of the data in the NDA are accurate."

Following discussion with the FDA at a Post-ODAC Meeting on March 11, 2019, the Applicant submitted a major amendment to NDA 212306 on March 13, 2019. The major amendment extended the user fee goal date to July 6, 2019.

The Applicant originally proposed the indication, XPOVIO, an oral XPO1 inhibitor, is indicated in

combination with dexamethasone, for the treatment of patients with relapsed refractory multiple myeloma who have received at least three prior therapies and whose disease is refractory to at least one proteasome inhibitor, at least one immunomodulatory agent, and an anti-CD38 monoclonal antibody, based on the results of from 122 patients treated in Part 2 of STORM. Following discussion with the Agency at the Post-ODAC Meeting, as part of the major amendment, the Applicant revised the proposed indication to include a narrower patient population based the results from a subpopulation of 83 patients from Part 2 of STORM who had 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 antibody.

3.3 Foreign Regulatory Actions and Marketing History

Selinexor is not currently marketed in any country.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

The Office of Scientific Investigations conducted inspections for study KCP-330-012 (STORM) at three clinical sites: Dr. David Dingli (site #16, 22 subjects), Dr. Dan Vogl (site #26, 16 subjects), and Dr. Sundar Jagannath (site #21, 34 subjects). The regulatory classification of Drs. Dingli and Vogl was No Action Indicated. The regulatory classification of Dr. Jagannath was Voluntary Action Indicated. The study data from these clinical sites, as reported by the Applicant to NDA 212306 are considered reliable.

4.2 Product Quality

The Office of Product Quality (OPQ) did not have any outstanding review issues and did not identify any potential risks to patient safety, product efficacy, or product quality that were not adequately mitigated. OPQ recommended approval of NDA 212306 and granted a (b) (4) re-test period for the selinexor drug substance and a 36-month expiration period for the drug product (b) (4)

4.3 Clinical Microbiology

Not applicable.

4.4 Devices and Companion Diagnostic Issues

No companion devices or diagnostics are included in the application.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Selinexor is an inhibitor of exportin 1 (XPO1) for the treatment of relapsed/refractory multiple myeloma (MM). Exportin 1 (CRM1/XPO1) is a karyopherin protein responsible for the facilitated export of nuclear export signal (NES)-containing cargo proteins and RNAs. XPO1 is overexpressed in a large variety of malignancies including MM. XPO1 exports over 200 different proteins out of the nucleus, including numerous tumor suppressor proteins [TSPs; e.g., p53, p73, retinoblastoma protein (pRb), Foxhead box O (FOXOs), adenomatous polyposis coli (APC), phosphatase and tensin homolog (PTEN)] and growth regulatory proteins [GRPs; e.g., nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor (IκB), p21, p27, surviving]. The established pharmacological class for selinexor is nuclear export inhibitor.

Selinexor binds covalently, but slowly reversibly, to the NES-binding groove of XPO1. In cell-based assays, selinexor inhibits XPO1-mediated nuclear export with an IC_{50}≈20 nM. XPO1 inhibition by selinexor leads to accumulation of TSPs/GRPs in the nucleus of cells, reduction of proto-oncogenes and inhibition of NF-κB signaling. These mechanisms have been demonstrated to be relevant to selinexor-mediated cell cycle arrest and apoptosis in MM cells. Selinexor dose dependently decreases viability of human MM cell lines with a median IC_{50} of 165 nM (n=12 cell lines). In vitro and in vivo (in the MM.1S xenograft model) studies were conducted to support the combination of selinexor with dexamethasone. In vivo, mean tumor volumes were lower in animals receiving selinexor or the combination of selinexor and dexamethasone than for animals treated with vehicle or dexamethasone alone. There was no statistically significant difference observed in tumor volume change AUC between the selinexor and selinexor plus dexamethasone groups.

The PK of selinexor after oral administration has been investigated in various animal species including, mice, rats, dogs, and monkeys. After oral administration, selinexor was absorbed from the gastrointestinal (GI) tract with median time to maximum plasma concentration (tmax) of 0.5 to 4.0 hours. The oral bioavailability of selinexor is 61% in rats and 68% in monkeys. In rats, [^{14}C]-selinexor distributes into the body with the highest concentrations being detected in the kidneys, liver, and small intestine. Following oral administration, unchanged selinexor is the most abundant drug-related compound found in systemic circulation. Multiple minor metabolites were observed in urine samples, suggesting selinexor metabolism by Phase 1 (oxidation, hydrolysis and N-dealkylation) and Phase 2 (conjugation with glucuronide and glutathione breakdown products). The majority of selinexor (≈75%) is excreted in the feces and to a lesser extent (≈16%) the urine. The elimination half-life (t½) following single oral doses of selinexor is 5.27 hours in the rat and 3.62 hours in the monkey.

Thirteen-week repeat-dose oral toxicity and toxicokinetic studies were conducted in the rat (0, 0.25, 1, or 4 mg/kg selinexor; 5 total doses given every 2-week period) and monkey (0, 0.1, 0.3, 1 mg/kg selinexor; 2 to 3 times/week) to support the NDA. Based on available data, both species were determined to be pharmacologically relevant for toxicology studies. The dose levels were adequately justified by treatment-related changes observed in animals on toxicology studies of shorter duration. TK data from the 13-week studies indicate that increases in exposures to selinexor were nearly proportional to increases in dose across the dose ranges studied. Decreased food intake leading to reduced body weights/weight loss was seen in both species. Rats exhibited toxicological sequalae due to hematopoietic/lymphoid hypoplasia and male/female reproductive organ effects. Female rats also exhibited higher liver weights and/or centrilobular hepatocellular hypertrophy and/or increased mitotic figures. Monkeys exhibited gastrointestinal effects and lymphoid/hematologic depletion. Aside from the effects on male reproductive tissues, the effects were somewhat reversible.

In the definitive embryo-fetal developmental (EFD) toxicity study, pregnant rats received selinexor at 0, 0.25, 0.75, or 2 mg/kg/day throughout organogenesis. Doses of 2 mg/kg/day were associated with toxicologically significantly reduced maternal body weights. Adverse developmental outcomes occurred at ≥ 0.75 mg/kg/day and included alterations to growth (e.g., fetal weights in the 0.75 and 2 mg/kg/day groups were 13.5% and 32.4% lower than controls) and structural abnormalities (such as incomplete or delayed ossification of sternebra(e) and/or vertebral arches, and/or unossified and bent ribs). The dose of 0.75 mg/kg/day in rats results in maternal exposures approximately 0.08-fold of human area under the curve (AUC) at the recommended dose of 80 mg. In the dose-finding EFD study in pregnant rats, all females in the 5 mg/kg/day group had 100% postimplantation loss, and consequently there were no viable fetuses available for evaluation. Based on its mechanism of action and findings from animal reproduction studies, the selinexor label will include a Warning and Precaution statement for embryo-fetal toxicity. Females of reproductive potential, and males with female partners of reproductive potential, will be advised to use effective contraception during treatment and for one week following the last dose of selinexor. In addition, the label will include a Use-in-Specific Populations statement regarding lactation; advising not to breastfeed. Breastfeeding is not recommended during treatment and for one week following the last dose.

Carcinogenicity studies were not conducted to support the use of selinexor for the proposed indication. Selinexor was not mutagenic in vitro in a bacterial reverse mutation (Ames) assay and was not clastogenic in both 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. Results from repeat-dose oral toxicity studies suggest selinexor may impair fertility in females and males of reproductive potential. 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 (AUC) in humans at the recommended human dose.

The nonclinical pharmacology/toxicology studies submitted to the NDA are adequate and there are no outstanding issues from a nonclinical perspective that would prevent approval of XPOVIO for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary pharmacology

A. In vitro studies

X-ray crystallography studies using Saccharomyces cerevisiae XPO1 containing a humanized NES-binding groove determined that selinexor binds in the groove at Cys528 in complex with other factors (i.e., HsRan-ScRanBP1). Selinexor forms a covalent bond with XPO1 through a warhead with an activated Michael acceptor in the Cα. Despite this covalent binding, selinexor acts as a slowly reversible inhibitor of XPO1. Experiments have shown preformed XPO-1-inhibitor complexes that are dialyzed for 24-hours to remove un- or de-conjugated selinexor results in partial restoration (up to 36% of control) of XPO-cargo interactions. Pull-down assays have shown that selinexor pretreatment inhibits the association of XPO1 with three different classical NESs/cargos (PKI-NES, MVM-NS2-NES, and full-length Snurportin).

Human osteosarcoma cells (U2OS) stably expressing green fluorescent protein-tagged HIV Rev response element with a protein kinase inhibitor NES (Rev-GFP) were used to determine an IC_{50} of ~20 nM for XPO1-dependent nuclear export of Rev-GFP. Immunofluorescence staining was used to show selinexor inhibited Rev-GFP nuclear export in human cells expressing wild type XPO relative to mutant XPO Cys528Ser cells. Cells with the Cys528Ser mutation were also more resistant in cytotoxicity assays.

Selinexor inhibited the export, resulting in nuclear accumulation, of tumor suppressor proteins (TSPs) and growth regulating proteins (GRPs); shown using immunohistochemistry in multiple myeloma cells. Selinexor also caused dose dependent cell death in multiple myeloma cell clines as measured by MTT assays providing a lowest IC_{50} of ~20 nM (range IC_{50} of ~20 nM-434 nM).

Sequestration in the nucleus resulted in functional activation and included molecules: p53, p21, FOXO3a, APC, FOXO1a, IκB, p27, monoclonal anti-protein phosphatase 2Aα (PP2Aα), and survivin. Functional activation of these molecules was assessed in cell cycle assays, showing transcriptional activation and phosphorylation of downstream targets and promotion of

apoptosis in MM1.S cells through cell cycle checkpoint regulation. Selinexor also inhibited the translation, cytoplasmic transport and capping of eIF4E proto-oncogenic mRNAs including: cyclin D, cyclin E, proto-oncogene, serine/threonine kinase (Pim1), ornithine decarboxylase (ODC), Mdm2, c-Myc, Bcl-2, and Bcl-6. Multiple myeloma cells treated with related compounds showed reduced protein expression of c-Myc, cyclin D, cyclin E, Mcl-1 and Bcl-XL. The in vitro activity of selinexor in combination with other drugs was evaluated in a series of cell-based assays. Proteasome inhibitor (PI) resistant and U226 PSR parent multiple myeloma cells were treated with either selinexor, bortezomib, or the combination and assessed for apoptosis by flow cytometry. The combination treatment demonstrated the highest activity against U226 parent cell line but not the U226 resistant cell line. Ex vivo bone marrow mononuclear cells and normal non-myeloma cells isolated from patients with myeloma refractory to PIs were treated with selinexor and bortezomib or carfilzomib in combination. The combination of PI and selinexor induced statistically significant apoptosis in bone marrow mononuclear cells relative to normal non-myeloma cells which had very little activity in response to the combination.

B. In vivo studies

The in vivo antitumor activity of selinexor was evaluated alone and in combination with dexamethasone in mouse xenograft models of multiple myeloma. In a MM1.S xenograft model in athymic nude mice, tumor-bearing mice were placed into groups (n=5 to 8/group), to receive vehicle (Groups 1 and 4), selinexor at 15 mg/kg (Group 2), or selinexor at 25 mg/kg (Groups 3 and 5) (Study: KS-0038). Mice were dosed two to three times per week. Tumor growth and body weight were measured twice a week for up to 60 days. Most of the vehicle animals were euthanized due to tumor burden. Animals treated with selinexor survived to the end of study, however body weight loss was notable for the animals receiving selinexor. Treatment with selinexor suppressed tumor growth compared to the vehicle control.

In a different xenograft model of multiple myeloma, NOD-SCID mice were implanted with H929 cells and were treated (n= 9/group) with vehicle (oral 3 times/week), dexamethasone alone at 1 mg/kg (intraperitoneal once daily), selinexor alone at 5 mg/kg (oral 3 times/week), or selinexor and dexamethasone at the same doses (Study: KS-0085). All animals survived until the end of the 30-day study. Body weight loss was notable throughout the study for the animals receiving the combination of selinexor and dexamethasone. Mean tumor volumes were lower in animals receiving selinexor or the combination of selinexor and dexamethasone than for animals treated with vehicle or dexamethasone alone. There was no statistically significant difference observed in tumor volume change AUC between the selinexor and selinexor plus dexamethasone groups.

Secondary Pharmacology

The potential for off-target activity was evaluated using a screening panel of 112 receptor or enzymatic targets (Study: KS-0034). 10 µM selinexor produced a 50% inhibition of MAO-B

oxidase. In a follow up functional assay with MAO-B oxidase, no IC_{50} could be determined for selinexor at 0.01 to 20 µM (Study: KS-0066). Selinexor had no toxicologically significant functional (agonist or antagonist) activity against the nicotinic receptor (Study: KS-0034), and IC_{50} values could not be calculated for the AurA/Aur2 kinase and p70s6K (Study: KS-0065).

Safety Pharmacology

Selinexor was evaluated for its ability to inhibit the hERG channel (IC_{50} = 20.6 µM) using whole cell patch clamp in stably-transfected HEK293 cells (Study: KS-0055). Cardiovascular endpoints were included in the 1 and 3-month GLP toxicology studies in monkeys, and included measurements of heart rate, blood pressure, and electrocardiogram (ECG) waveforms (and PR, RR, QRS, QT, and QTcB intervals). There was no evidence of drug-related changes on cardiovascular endpoints. Respiratory function was assessed by whole body plethysmography following single oral doses of 0, 2, 10, or 50 mg/kg selinexor in Sprague-Dawley rats (Study: KS-0054). Administration of ≥10 mg/kg resulted in statistically significant lower respiratory frequency, tidal volume, and minute volume through 300 minutes post-dosing. Selinexor was evaluated in an Irwin Test for effects on central nervous system function (Study: KS-0051). Sprague Dawley rats received single oral doses of 0, 2, 10, or 50 mg/kg selinexor, and gross behavioral, physiological, and neurological state observations of the animals were monitored for 300 minutes post-dose. Administration of 50 mg/kg selinexor resulted in statistically significant decreases in body temperature that resolved by the final observation time point (24 hours).

5.4. ADME/PK

Table 3: Summary of ADME/PK Studies

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td colspan="2">Absorption</td></tr>
<tr><td>Pharmacokinetics and Brain Penetration of KPT-330 Following Single Intravenous and Oral Administration to Male Sprague-Dawley Rats (KS-0020)</td><td>Bioavailability of selinexor was assessed in the rat using single oral (PO) and intravenous (IV) doses.
<table>
<tr><td></td><td>Cmax (ng/mL)</td><td>AUC_t (ng*hr/mL)</td><td>Bioavailability %</td></tr>
<tr><td>5 mg/kg IV</td><td>8660</td><td>5567</td><td>NA</td></tr>
<tr><td>10 mg/kg PO</td><td>5570</td><td>6813</td><td>61.2</td></tr>
</table>
<table>
<tr><td>Regimen</td><td>Brain: Plasma</td></tr>
<tr><td>10 mg/kg PO</td><td>0.719</td></tr>
</table></td></tr>
<tr><td>Pharmacokinetics of KPT-330 Following Single Intravenous and Oral Administration to Male Cynomolgus Monkeys (KS-0036)</td><td>Bioavailability of selinexor was assessed in the monkey using single oral (PO) and intravenous (IV) doses.
<table>
<tr><td></td><td>Cmax (ng/mL)</td><td>AUC_t (ng*hr/mL)</td><td>Bioavailability %</td></tr>
<tr><td>2 mg/kg IV</td><td>1720</td><td>1490</td><td>NA</td></tr>
</table></td></tr>
</table>

Type of Study	Major Findings			
	10 mg/kg PO	2110	4420	67.5
Distribution				
Pharmacokinetics, Quantitative Whole-Body Autoradiography Tissue Distribution, and Excretion Balance in Rats following a Single Oral (Gavage) Dose of [^{14}C]-KPT-330 (KS-0091)	Tissue distribution was evaluated in the rat following administration of a single 5 mg/kg oral dose of [^{14}C]-selinexor. Quantitative whole-body autoradiography was evaluated for up to 168 hours (1 week) post-dose. The highest concentrations of radioactivity were observed in the kidneys, liver, and small intestine. There was no specific binding to pigmented tissues. Very low-concentrations were detectable at 168 hours post-dose, and much of the dose was eliminated by 24 hours. Distribution to the brain was observed.			
Metabolism				
Pharmacokinetics, Quantitative Whole-Body Autoradiography Tissue Distribution, and Excretion Balance in Rats following a Single Oral (Gavage) Dose of [^{14}C]-KPT-330 (KS-0091)	The metabolism of KPT-330 was also assessed in this study. Unchanged selinexor was the most abundantly detected compound at up to 91% through 8 hours. Most of the radioactivity was eliminated in the feces (54-87%) and urine (approximately 27%) by 168 hours post-dose.			
Metabolite Identification of Selinexor in Monkey Plasma (KS-50015)	Selinexor was detected as the most abundant drug related component in all post-dose samples (out to Day 40). The primary metabolic pathways were oxidation. glucuronidation (M6), N-dealkylation (M7, KPT-452), amide hydrolysis (M9), N-dealkylation in combination with oxidation (M4). Additionally, direct N-glucuronidation (M5), cysteine conjugation (M1), cysteinylglycine conjugation (M3) and glutathione conjugate (M2).			
Elimination				
Pharmacokinetics, Quantitative Whole-Body Autoradiography Tissue Distribution, and Excretion Balance in Rats following a Single Oral (Gavage) Dose of [^{14}C]-KPT-330 (KS-0091)	Most of the radioactivity was eliminated in the feces (54-87%) and urine (approximately 27%) by 168 hours post-dose.			
Study KS-0020 and KS-0036	The elimination half-life (t½) following single oral doses of selinexor is 5.27 hours in the rat and 3.62 hours in the monkey.			

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: A 13-Week (13-Cycle) Oral Gavage Toxicity and Toxicokinetic Study of KPT-330 in Sprague Dawley Rats with a 4-Week Recovery Period/ KNC-G-13-001

Key Study Findings

- There were no unscheduled deaths.
- Hematological changes included decreased eosinophils and/or monocytes, and decreased platelet counts.
- Target organs were male and female reproductive organs, adrenal cortex, bone marrow, and lymphoid organs.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0.25, 1, 4 mg/kg; test article was administered 3 days on/4 off, weekly for 13 weeks
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4)
Species/Strain:	Sprague Dawley [Crl:CD(SD)] rats
Number/Sex/Group:	15 sex/main study group, 9sex/TK group
Age:	7 weeks
Satellite groups/ unique design:	No/No
Deviation from study protocol affecting interpretation of results:	The reported deviations did not affect study interpretability.

Observations and Results

Table 4: General Toxicology Study (KNC-G-13-001)

Parameters	Major findings ((%) change relative to concurrent controls)
Mortality	None
Clinical Signs	Unremarkable
Body Weights	HD: males (-5.5%), females (-10.3%)
Ophthalmoscopy	Unremarkable
Hematology	***LD:*** *Decreased Eosinophils males (-31%) ** ***MD****: Decreased Platelets males (-27%) females (-25%) ** *Decreased APTT males (-9%) ** *Decreased Eosinophils males (-31%) ** ***HD:*** *Decreased Platelets males (-41%) females (-31%) ** *Decreased APTT males (-13%) **

<table>
<tr><td></td><td>Decreased Eosinophils males (-68%) *
Increased Monocytes females (100%) *

Decreased Eosinophils (through recovery males -33%) *</td></tr>
<tr><td>Clinical Chemistry</td><td>HD: Decreased total protein males (-8%) *
Decreased globulin males (-8%) *
Decreased glucose males (-12%) females (-20%) *
Dose dependent decrease in creatinine down to males (-24%) females (-24%) in HD animals*</td></tr>
<tr><td>Urinalysis</td><td>Unremarkable</td></tr>
<tr><td>Gross Pathology</td><td>Small and soft testes, small epididymis, clear fluid in the uterus, small thymus.</td></tr>
<tr><td>Organ Weights</td><td>Treatment with selinexor was associated with an increase in absolute, body and brain-weight relative uterus liver and adrenal glands and a decrease seminal vesicle, thymus, pituitary weights. These changes are relatively small in magnitude. Severe reductions in testes (~50% relative to body and brain weight) and epididymides (~37 and 40 % relative to body and brain weight) were noted in high dose animals and changes persisted through the recovery period.</td></tr>
<tr><td>Histopathology Adequate battery: Yes</td><td>See table below for a summary of major findings.</td></tr>
<tr><td>Toxicokinetics</td><td>• Peak exposure (Cmax) and overall (AUC_{last}) exposures were approximately dose-proportional over the 16-fold dose-range on Day 0 in males and females.
• Exposures in female rats were generally minimally higher (Cmax or AUC_{last}), than in males.
• There was no meaningful evidence of accumulation.
<table>
<tr><th rowspan="2">Dose</th><th colspan="2">AUC_{last} (ng•hr/mL)</th><th colspan="2">C_{max} (ng/mL)</th><th colspan="2">T_{max} (hr)</th></tr>
<tr><th>Day 0</th><th>Day 88</th><th>Day 0</th><th>Day 88</th><th>Day 0</th><th>Day 88</th></tr>
<tr><td><u>Males</u></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>0.25 mg/kg</td><td>112</td><td>134</td><td>28.5</td><td>48.6</td><td>1</td><td>0.25</td></tr>
<tr><td>1 mg/kg</td><td>584</td><td>592</td><td>113</td><td>152</td><td>0.5</td><td>0.25</td></tr>
<tr><td>4 mg/kg</td><td>2060</td><td>2520</td><td>503</td><td>577</td><td>1</td><td>0.5</td></tr>
<tr><td><u>Females</u></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>0.25 mg/kg</td><td>136</td><td>194</td><td>34.4</td><td>61.2</td><td>1</td><td>0.5</td></tr>
<tr><td>1 mg/kg</td><td>544</td><td>811</td><td>166</td><td>258</td><td>0.5</td><td>0.5</td></tr>
<tr><td>4 mg/kg</td><td>2390</td><td>2730</td><td>659</td><td>602</td><td>0.5</td><td>0.5</td></tr>
</table>
(Excerpted from Applicant's Submission)</td></tr>
</table>

Abbreviations: LD = low dose; MD = mid dose; HD = high dose.
(-) indicates reduction in parameters compared to control.
* Statistically significant change relative to concurrent control.

Table 5: Major Histopathology Findings in Rat

Sex		Male				Female			
Group (mg/kg)	severity	0	0.25	1	4	0	0.25	1	4
Number of animals evaluated		15	15	15	15	15	15	15	15
Testes; degeneration, tubule	minimal		2	1					
	mild			2					
	severe			1	10				
;degeneration, germ cell	minimal		4						
	mild		3	8					
	moderate			2					
;retention, spermatids	minimal		4						
	mild		2	6					
	severe		0	4					
Epididymis; reduced sperm luminal	minimal		2	5					
	moderate			1					
	severe				10				
Seminal vesicles; decreased secretion	minimal			1	3				
	moderate		1	0	2				
Ovaries; increased corpus lutea	minimal							1	1
	mild							1	2
Spleen; depletion lymphoid follicles	minimal				1			1	3
	mild				2				
; depletion, marginal zone	minimal			1				1	3
	mild			2	3			1	6
	moderate			1	6				
	severe				1				
;depletion, periarteriolar lymphoid sheath	minimal				2				
	mild				1				
Adrenal Cortex; hypertrophy	minimal			3	2			3	6
	mild				7				
Bone Marrow, Sternum; hypocellular	minimal			5	5				

(Source: FDA Analysis of Study KNC-G-13-001)

Study title/ number: A 13-Week (13-Cycle) Oral (Nasogastric) Toxicity and Toxicokinetic Study of KPT-330 in Cynomolgus Monkeys with a 4-Week Recovery Period/ KNC-G-13-002

Key Study Findings

- There were no unscheduled deaths during the study.
- There were decreases in red cell parameters, platelets, monocytes and WBCs.
- Target organs included the lymphoid organs (spleen, thymus, lymph nodes), which exhibited lymphoid depletion.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0.1, 0.3, or 1 mg/kg Each dosing cycle was 1 week, consisting of combinations of 3 dosing and 4 non-dosing days, or 2 dosing and 5 non-dosing days, with the pattern rotated each week
Route of administration:	Oral nasogastric intubation
Formulation/Vehicle:	(b) (4)
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	6 sex/group
Age:	2.3 to 3.3 years old
Satellite groups/ unique design:	No/No
Deviation from study protocol affecting interpretation of results:	The reported deviations do not appear to have affected overall study interpretation.

Observations and Results

Table 6: General Toxicology Study KNC-G-13-002

Parameters	Major findings ((%) change relative to controls)
Mortality	None
Clinical Signs	**LD, MD, HD**: Thin body appearance, inappetence, dermal atonia, and diarrhea.
Body Weights	Dose dependent decrease in body weight gain up to 7.3% and -8.4% in males and females respectively at **HD**.
Ophthalmoscopy	Unremarkable
ECG	Unremarkable
Hematology	**HD:** Decreased red blood cells males (-16%) **HD**: Decreased reticulocytes females (-33%) **HD**: Decreased monocytes females (-56%) Dose dependent decrease in platelets up to -31% (males) at **HD*** Dose dependent decrease in WBC up to -37% (females) at **HD***
Clinical Chemistry	Unremarkable
Urinalysis	Unremarkable
Gross Pathology	**HD**: Reduced thymus size
Organ Weights	**HD**: Reduced thymus weights (absolute and relative to final body weight and/or brain weight, males). **MD**: reduced thymus weights (absolute and relative to final body weight and/or brain weight, females)
Histopathology **Adequate battery:** Yes	See table below for a summary of major findings.
Toxicokinetics	• Peak exposure (Cmax) and overall (AUC_{last}) exposures were approximately dose-proportional over the 10-fold dose-range on Day 0 in males and females.

	• There were no gender related effects on exposure (Cmax or AUC_{last}). • There was no evidence of accumulation.

Dosage	AUC_{last} (ng•hr/mL)		C_{max} (ng/mL)		T_{max} (hr)	
	Day 0	Day 88	Day 0	Day 88	Day 0	Day 88
Males						
0.1 mg/kg	143	133	22.2	25.5	2.0	1.8
0.3 mg/kg	528	440	105	83.5	1.4	1.5
1 mg/kg	1820	1690	285	247	1.7	2.3
Females						
0.1 mg/kg	153	131	33.5	29.7	0.92	1.7
0.3 mg/kg	505	434	117	106	1.0	1.1
1 mg/kg	1660	1320	284	230	1.5	1.7

(Excerpted from Applicant's Submission)

Abbreviations: LD = low dose; MD = mid dose; HD = high dose.
(-) Indicates reduction in parameters compared to control.
* Statistically significant change relative to concurrent control.

Table 7: Major Histopathology Findings in Monkey

Sex		Male				Female			
Group (mg/kg)	severity	0	0.1	0.3	1	0	0.1	0.3	1
Number of animals evaluated		6	6	6	6	6	6	6	6
Spleen, lymphoid depletion	minimal				1		1	1	1
Thymus, reduced cellularity	mild				3				1
Lymph nodes, axillary, lymphoid depletion	minimal				1				

(Source: FDA Analysis of Study KNC-G-13-002)

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: Bacterial Reverse Mutation (Ames) Test/ KS-0039

Key Study Findings:

- Selinexor did not increase the mean number of revertant colonies either in the presence or absence of metabolic activation; thus, the study was negative for induction of reverse mutations.

GLP compliance: Yes

Test system: TA98, TA100, TA1535, TA1537, WP2uvrA; 1.58, 5.0, 15.8, 50, 158, 500, 1581, and 5000 µg/plate (limit dose based on absence of toxicity and precipitation).

Study is valid: The positive control assay demonstrated sensitivity of the systems and both the positive and negative control assays induced the expected mean number of revertant colonies; thus, the criteria for a valid test were met.

In Vitro Assays in Mammalian Cells

Study title/ number: Chromosome Aberration Test/ KNC-G-13-005
Key Study Findings:

- Selinexor did not significantly increase the number of chromosomal aberrations and there were no observed increases in numerical aberrations (percent of cells with polyploidy/endoreduplication).

GLP compliance: Yes
Test system: human peripheral blood lymphocytes; up to 0.5 ug/mL; +/-S9
Study is valid: The positive control assay demonstrated sensitivity of the systems and both the positive and negative controls performed as expected.

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)
Study title/ number: Micronucleus Test in Rat/ KNC-G-13-004
Key Study Findings:

- Selinexor was negative for induction of polychromatic erythrocytes (MNPCEs) following administration of oral doses up to 10 mg/kg/ day for 3 consecutive days in Sprague Dawley rats.

GLP compliance: Yes
Test system: Male and female Sprague Dawley rats
Study is valid: The positive control assay demonstrated sensitivity of the system and both the positive and negative control assays induced the expected mean number of micronucleated polychromatic erythrocytes (MNPCEs) in the bone marrow; thus, the criteria for a valid test were met.

5.5.3. Reproductive and Developmental Toxicology

Embryo-Fetal Development
Study title/ number An Oral (Gavage) Study of the Effects of KPT-330 on Embryo/Fetal Development in Rats/ KNC-G-13-008
Key Study Findings

- NOAEL for maternal toxicity was 0.25 mg/kg/day (GD 17: AUC_{last} value of 0.121 µg•h/mL and C_{max} value of 0.034 µg/mL).
- Doses of ≥0.75 mg/kg (≥4.5 mg/m^2) caused skeletal variations, consisting of incomplete or delayed ossifications and reduced fetal weight.
- Doses of ≥2 mg/kg (≥12 mg/m^2) caused post-implantation loss.

Conducting laboratory and location	
GLP compliance:	(b) (4)
Methods	
Dose and frequency of dosing:	0.25, 0.75, or 2 mg/kg/day (0, 1.5, 4.5, or 12 mg/m^2/day)
Route of administration:	Oral gavage

Formulation/Vehicle:	(b) (4)
Species/Strain:	Sprague Dawley [Crl:CD(SD)] rats
Number/Sex/Group:	25 time-mated dams/Group
Satellite groups:	8 toxicokinetic dams/Group
Study design:	Time-mated females received KPT-330 on GDs 6-17, corresponding to the period of implantation through the closure of the hard palate. • Laparohysterectomies were performed on Day 20. • Uteri, placentae, and ovaries were examined and weighed. • Fetuses, total implantations, late and early resorptions, and corpora lutea were examined and recorded. • Fetuses were weighed, sexed, and examined for external, visceral, and skeletal malformations and variations. • TK was collected from 4 animals per group on Days 6 ad 17.
Deviation from study protocol affecting interpretation of results:	The reported deviations do not appear to have affected overall study interpretation.

Observations and Results

Table 8: Reproductive and Developmental Toxicology Study (KNC-G-13-008)

Parameters	Major findings
Mortality	None
Clinical Signs	Unremarkable
Body Weights	Lower mean body weight gains relative to the control were noted throughout the treatment period and post-treatment period. MD: On GD 20, mean body weights at 0.75 were -5.2%. HD: On GD 20, mean body weights at 2 mg/kg/day were -11.8% ($p<0.05$) vs. the control group. Reduced mean net body weight and net body weight gain were noted at 2 mg/kg/day ($p\leq0.01$)
Necropsy findings Cesarean Section Data	MD: Significantly reduced ($p<0.01$) mean gravid uterine weights were lower at ≥0.75 mg/kg/day (lower fetal weights were noted at these doses). Post implantation loss occurred at doses of ≥0.75 mg/kg (≥12 mg/m^2) at 10.7% per litter.

Summary of fetal malformations

Dose (mg/kg)	0	0.25	0.75	2
Number of fetuses/litters evaluated	368/23	361/25	349/24	334/23
External				
Microphthalmia (left)				1
Localized fetal edema (neck and thorax)				1
Visceral				
Malpositioned kidney				1
Persistent truncus arteriosis				1
Accesory lobules of the liver	2		2	6
Hydrocephaly		1		

Summary of fetal variations

Dose (mg/kg)	0	0.25	0.75	2
Number of fetuses/litters evaluated	368/23	361/25	349/24	334/23
Reduced ossification of the 13th rib	1	2	6	4
Unossified and reduced ossification of the vertebral arches		3	5*	22*
Unossified sternebrae 1, 2, 3, 4			1	14*
Unossifed sternebrae 5, 6	26	66	93	236
Bent ribs	2	0	1	7

Toxicokinetics

Peak (Cmax) and overall (AUC) exposures were approximately dose-proportional over the 8-fold dose-range. There was no evidence for accumulation on Days 6 and 17.

KPT-330 Dosage (mg/kg/day):	0.25	0.75	2
Gestation Day 6			
AUC_{last} (ng•hr/mL)	137	418	1060
C_{max} (ng/mL)	36.1	96.4	351
T_{max} (h)	1	1	1
$T_{1/2}$ (hr)	2.4	2.8	3.7
Gestation Day 17			
AUC_{last} (ng•hr/mL)	121	446	1660
C_{max} (ng/mL)	34.1	124	305
T_{max} (h)	1	1	1
$T_{1/2}$ (hr)	2.4	3.3	3.5

Abbreviations: LLOQ = lower limit of quantitation, AUC_{last} = area under curve from time of dosing to last observation > LLOQ, C_{max} = maximum observed concentration, T_{max} = sampling time of C_{max}, $T_{1/2}$ = terminal half-life

(Excerpted from Applicant's Submission)

*Exceeds the maximum range of the laboratory's historical control
Abbreviations: LD = low dose; MD = mid dose; HD = high dose

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6 Clinical Pharmacology

6.1 Executive Summary

The efficacy and safety of selinexor in adult patients with relapsed or refractory multiple myeloma (RRMM) was evaluated in 2 studies, including one open-label, single-arm phase 1/2b Study KCP-330-012 and one phase 1, open-label, dose-escalation Study KCP-330-001. Part 2 of Study KCP-330-012, with a prespecified subgroup analysis of the 83 patients with RRMM who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors (PIs), at least two immunomodulatory agents (IMiDs), and an anti-CD38 monoclonal antibody (mAb), was used as registrational trial. The proposed starting dose of selinexor is 80 mg (four 20 mg tablets) orally in combination with dexamethasone on days 1 and 3 of each week with or without food. At the proposed starting dose, 99.1% patients had treatment-emergent adverse event (TEAE) that resulted in dose modification, 26.8% patients had TEAE that resulted in treatment discontinuation, and the median duration on the proposed 80 mg dose was 3.5 weeks during Part 2 of KCP-330-012. Exposure-response analysis for safety indicates a relationship between higher exposures and higher incidences of adverse events. While the study showed an ORR of 25.3% in patients with RRMM who have received at least four prior therapies and whose disease is refractory to at least two PIs, at least two IMiDs, and an anti-CD38 mAb; the high rates of TEAE, and poor tolerability indicate the proposed dosing regimen is not well tolerated. A PMR to inform on the optimal dose for selinexor in this patient population will be issued.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 212306. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The pivotal efficacy of selinexor in a subpopulation of patients with RRMM who have received at least four prior therapies and whose disease is refractory to at least two PIs, at least two IMiDs, and an anti-CD38 mAb was evaluated in Part 2 of Study KCP-330-012. Supportive evidences of effectiveness were evaluated in Study KCP-330-012 and Study KCP-330-001.
General dosing instructions	The proposed starting dose of selinexor is 80 mg (four 20 mg tablets) orally in combination with dexamethasone on days 1 and 3 or each week with or without food. The proposed

	dosing is not tolerated. Exposure-response analysis for safety indicates that lower doses may be better tolerated. See Post-Marketing Requirements and Commitments for PMR regarding alternative lower doses.
Dosing in patient subgroups (intrinsic and extrinsic factors)	▪ There is limited pharmacokinetics (PK) understanding of selinexor in patients with moderate or severe hepatic impairment. See Post-Marketing Requirements and Commitments for PMR regarding moderate or severe hepatic impairment. ▪ There is limited PK understanding of selinexor as a CYP3A4 substrate. See Post-Marketing Requirements and Commitments for PMR and PMC regarding selinexor as a CYP3A4 substrate.
Labeling	Generally acceptable. The review team has specific content and formatting change recommendations.
Bridge between the to-be-marketed and clinical trial formulations	To-be-marketed product (TF2.3) (b) (4) second-generation tablet formulation 2 (TF2.2) used in registration trial except (b) (4) The applicant provided in vitro dissolution data to demonstrate BE between TF2.3 and TF2.2.

Post-Marketing Requirements and Commitments

3657-2: Conduct a randomized phase 2 clinical trial of selinexor in combination with dexamethasone to characterize the safety and efficacy of at least two different doses of selinexor, which are lower than the dosing regimen of 80 mg on Days 1 and 3 of each week, in patients with relapsed refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody. The primary objective is to assess the overall response rate in all treatment arms according to International Myeloma Working Group (IMWG) criteria by investigator assessment. The trial should include one interim analysis for futility. The results of this trial will be used to inform the optimal dose for selinexor in this patient population. Submit a final report with full datasets.
Preliminary Protocol Submission to Include SAP: 08/2019
Final Protocol Submission: 10/2019
Interim Analysis: 12/2020
Trial Completion: 06/2021
Final Report Submission: 10/2021

3657-3: Conduct a hepatic impairment trial in patients with NCI classification of moderate, severe hepatic impairment or Child-Pugh classes B, and C compared to patients with normal hepatic function since drug clearance may be reduced with hepatic impairment.
Preliminary Protocol Submission: 08/2019
Final Protocol Submission: 09/2019
Trial Completion: 03/2021
Final Report Submission: 09/2021

3657-4: Conduct a drug interaction trial in patients to evaluate the effect of coadministration of a strong CYP3A4 inhibitor on the pharmacokinetics of selinexor.
Preliminary Protocol Submission: 08/2019
Final Protocol Submission: 09/2019
Trial Completion: 03/2021
Final Report Submission: 09/2021

3657-5: Conduct a dedicated drug interaction trial in patients to determine the effect of coadministration of a strong CYP3A4 inducer on the pharmacokinetics of selinexor.
Preliminary Protocol Submission: 09/2020
Final Protocol Submission: 03/2021
Trial Completion: 03/2022
Final Report Submission: 09/2022

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Selinexor exhibited dose-proportional increases in exposure across the dose range of 3 mg/m^2 to 85 mg/m^2 following both single dose and repeated doses on days 1 and 3 of each week. Selinexor mean half-life ($t_{1/2}$) is 6 to 8 hours. No clinically relevant accumulation at steady-state was observed after repeated doses on days 1 and 3 of each week. Following a single 80 mg administration, the mean (±SD) peak plasma concentration (C_{max}) was 680 (124) ng/mL (~ 1.5 µM) and the mean AUC was 5386 (1116) ng•h/mL.

ADME Properties

Absorption: The time to reach C_{max} (T_{max}) following selinexor administration is within 4 hours. Absolute bioavailability has not been determined. Selinexor showed no clinically significant food effect.

Distribution: The population PK analysis estimated apparent volume of distribution is 125 L. Plasma protein binding is 95%. Blood-to-plasma ratio ranges from 0.63 to 0.69 for selinexor concentrations ranges from 0.01 to 10 µM.

Metabolism: Selinexor is mainly metabolized by oxidation and conjugation to glucuronidation and glutathione-related metabolites. The oxidation is catalyzed primarily by CYP3A4. UDP-glucuronosyltransferases (UGTs) and glutathione S-transferases (GSTs) involve in conjugation pathways.

Elimination: The mean (%CV) of the apparent plasma clearance was 17.9 L/h (15.9%).

Excretion: There is no human mass balance study in the NDA submission. Selinexor is excreted by the hepatobiliary route in feces with minimal excretion in urine based on cumulative data from 14C mass balance study in rats. In human feces, the predominant metabolite observed was N-dealkylation, which is catalyzed by CYP3A4. In human urine, the primary metabolite observed was cysteine adduct, which is catalyzed by GST.

6.2.2 General Dosing and Therapeutic Individualization

General Dosing

The proposed starting dose of selinexor is 80 mg (four 20 mg tablets) orally in combination with dexamethasone (selinexor in combination with dexamethasone is referred as Sd in the review) on days 1 and 3 or each week with or without food. At the starting dosing regimen, 88.6% patients had TEAE that resulted in dose modification and 28.5% patients had TEAE that resulted in treatment discontinuation. The exposure-response analysis indicates a relationship between higher exposures and adverse events suggesting that lower doses may be better tolerated.

Therapeutic Individualization

Specific Populations

Patients with Hepatic Impairment: The apparent clearance of selinexor was not substantially altered in patients with mild hepatic impairment at baseline (N = 100 for mild) compared to patients with normal hepatic function (see Section 13.3.4 for detail). There was insufficient data to assess the impact of moderate and severe hepatic impairment on the PK of selinexor. Given the limited numbers of patients with moderate/severe hepatic impairment (N = 6 for moderate, N = 3 for severe), FDA will issue a PMR to conduct a clinical trial to determine PK of selinexor in patients with moderate and severe (b) (4) impairment. Refer to Post-Marketing Requirements and Commitments for detail.

Patients with Renal Impairment: The apparent clearance of selinexor was not substantially altered in patients with various degrees of renal impairment at baseline (N = 277 for mild, N =167 for moderate, N = 15 for severe) compared to patients with normal renal function (see Section 13.3.4 for detail). No dose adjustment for selinexor is recommended for patients with renal impairment.

Drug-Drug Interactions (DDIs)
Selinexor is mainly metabolized by oxidation and conjugation to glucuronidation and glutathione-related metabolites. The oxidation is catalyzed primarily by CYP3A4. UGTs and GSTs may be involved in conjugation pathways. There are potential DDIs between selinexor and CYP3A4 inhibitors or inducers. The DDI potential between selinexor and CYP3A4 modulators were not characterized in vivo. FDA will issue a PMR to conduct a clinical trial to determine effect of strong inhibitors and inducers of CYP 3A4 on the PK of selinexor. Refer to Post-Marketing Requirements and Commitments for detail.

Outstanding Issues

We will issue (b) (4) PMRs and one PMC. Refer to Post-Marketing Requirements and Commitments for details.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Table 9: General Pharmacology and Pharmacokinetics

Pharmacology	
Mechanism of Action	Selinexor is an oral exportin 1 (XPO1) inhibitor
Active Moieties	Selinexor is the major circulating moiety in human plasma. No major active metabolites are identified. The most common circulating metabolite is the trans-isomer of selinexor, which has ~10% of the XPO1 inhibiting activity of selinexor.
QT Prolongation	Selinexor had no large effect (i.e. no greater than 20 ms) on QTc interval at the therapeutic dose level.
General Information	
Bioanalysis	Selinexor and its major metabolite in plasma were measured using validated LC/MS/MS methods. A summary of the method validation reports is included as an appendix (13.3.1).
Healthy Volunteers vs. Patients	Selinexor has not been studied in healthy volunteers.
Drug exposure at steady state following the therapeutic dosing regimen	AUC and C_{max} were determined based on intensive PK sampling in Study KCP-330-001 in patients at the 45 mg/m^2 (~80 mg). Following one single dose (Cycle 1 Day 1), the AUC_{INF} and C_{max} (mean (CV%)) were 5390 (21%)·h/mL and 680 (18%) ng/mL, respectively. Following multiple doses (Cycle 1 Day 15/17), the AUC_{0-8h} and C_{max} (mean (CV%)) were 2680 (12%)·h/mL and 540 (23%) ng/mL, respectively. See section 13.3.2 for detail.
Minimal effective dose or exposure	Not available. The proposed starting dose of selinexor is 80 mg orally in combination with dexamethasone on days 1 and 3 or each week is the lowest dose level studied for selinexor when administered in combination with dexamethasone.
Maximal tolerated dose	Selinexor 120 mg on days 1 and 3 or each week as a monotherapy

Dose Proportionality	Selinexor showed dose-proportional increase in exposure with increasing doses the dose range of 3 mg/m^2 to 85 mg/m^2 following both single dose and repeated doses on days 1 and 3 of each week. See section 13.3.2 for detail.		
Accumulation	No clinically relevant accumulation at steady-state was observed after repeated doses on days 1 and 3 of each week.		
Variability	In patients after 45 mg/m^2 (~80 mg) multiple doses, CV% for Cmax is 23% and for $AUC_{0\text{-}8h}$ is 12%.		
Absorption			
Oral	Absolute oral bioavailability has not been determined		
Bioequivalent (BE) Tablets TF2.2/TF2.3 formulation	To-be-marketed product (TF2.3) (b) (4) the clinical second-generation tablet formulation 2 (TF2.2 used in registration trial) except (b) (4) The applicant provided in vitro dissolution data to demonstrate BE between TF2.3 and TF2.2. See Biopharmaceutics review by Dr. Akm Khairuzzaman (http://panorama.fda.gov/document/view?ID=5c1cf23f0062c0036d8283bef7beee9f&activeTab=tab-document-approvals&mode=anaconda) for detail.		
Bioequivalent (BE) Tablets TF1/TF2.2 formulation GMR (90% CI)	No clinically relevant difference between tablets TF1 and TF2.2 formulation		
	Cmax	AUC_{last}	AUC_{INF}
	1.03 (0.817, 1.30)	1.04 (0.999, 1.09)	1.04 (0.999, 1.09)
Bioequivalent (BE) Tablets TF2.2/Oral Suspension formulation GMR (90% CI)	No clinically relevant difference between tablets TF2.2/Oral Suspension		
	Cmax	AUC_{last}	AUC_{INF}
	0.842 (0.657, 1.08)	0.939 (0.896, 0.984)	0.943 (0.900, 0.988)
Oral T_{max}	The T_{max} was between 1 and 4 hours		
Food effect* for Tablets TF1 formulation Fasted/fed GMR (90% CI)	No clinically relevant food effect		
	Cmax	AUC_{last}	AUC_{INF}
	1.15 (0.888, 1.48)	1.16 (1.04, 1.28)	1.16 (1.05, 1.26)
Substrate transporter systems [in vitro]	Not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2-K		
Distribution			
Volume of Distribution	Mean apparent volume of distribution at steady-state (Vss/F) is 125 L		
Plasma Protein	95%		

Blood to Plasma Ratio	0.63 to 0.69
Elimination	
Half-life	The geometric mean plasma half-life ranged from 4-6 hours
Clearance	The geometric mean (%CV) apparent clearance (CL/F) at steady-state: 17.9 L/hr (15.9%)
Metabolism	
Primary metabolic pathway(s)	Selinexor is mainly metabolized by oxidation and conjugation to glucuronidation and glutathione-related metabolites. The oxidation is catalyzed primarily by CYP3A4. UGTs and GSTs involve in conjugation pathways.
Inhibitor/Inducer	Selinexor is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4/5. Selinexor is not a CYP3A4, CYP1A2, or CYP2B6 inducer. In vitro, selinexor inhibits OATP1B3 with an IC_{50} value of 6.20 µM. Selinexor may inhibit OATP1B3 in vivo based on R > 1.1.
Excretion	
Primary excretion pathways	There is no human mass balance study in the NDA submission. Selinexor is excreted by the hepatobiliary route in feces with minimal excretion in urine based on cumulative data from ^{14}C mass balance study in rats. In human feces, the predominant metabolite observed was N-dealkylation, which is catalyzed by CYP3A4. In human urine, the primary metabolite observed was cysteine adduct, which is catalyzed by GST.

6.3.2 Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Selinexor has not demonstrated single agent activity in patients with RRMM. The primary evidence of effectiveness, ORR per Independent Review Committee (IRC), was obtained from Part 2 of Study KCP-330-012 using a prespecified subgroup analysis of the 83 patients who had received at least four prior therapies and whose disease is refractory to at least two PIs, at least two IMiDs, and an anti-CD38 mAb.

Study KCP-330-012 was a multicenter, single-arm, 2-part, open-label study designed to evaluate the efficacy and safety of Sd in patients with quad-exposed, double-class-refractory or penta-exposed, triple-class-refractory MM. The Study includes Part 1 and Part 2. Details regarding the Study KCP-330-012 are provided in Section 7.2.1. Part 2 enrolled 123 patients with penta-exposed (defined as patients who previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab (and an alkylating agent)), triple-class-refractory MM (defined as patients whose disease is refractory to prior treatment with at least one IMiD, at least one PI, and the anti-CD38 mAb daratumumab (and glucocorticoids)).

The efficacy assessment was conducted in 83 patients in Part 2 of Study KCP-330-012 who had received at least four prior therapies and whose disease is refractory to at least two PIs, at least two IMiDs, and an anti-CD38 mAb. This population is referred to as the BCLPD-R (bortezomib-,

carfilzomib-, lenalidomide-, pomalidomide-, daratumumab-refractory) population. All patients received selinexor 80 mg PO in combination with low-dose dexamethasone 20 mg twice-weekly on Days 1 and 3 for every week (the proposed starting dosing regimen). The ORR in the BCLPD-R population was 25.3% (21 out of 83). Additional details regarding the evaluation of the efficacy endpoints in Study KCP-330-012 are provided in Section 7.2.3.

The additional evidence of effectiveness was obtained from the remaining patients in Part 2 and Part 1 of Study KCP-330-012 as well as phase 1 Study KCP-330-001. Study KCP-330-001 was a Phase 1 study conducted in 286 patients with various hematologic malignancies, including 81 patients with RRMM. Patients with RRMM were administered selinexor doses ranging from 3 mg/m^2 to 60 mg/m^2. Details regarding the Study KCP-330-001 are provided in Section 7.2.4. For all patients with RRMM (n = 81), the ORR was 8.6% (95% CI: 4, 17). ORR was only observed at selinexor in combination with dexamethasone and selinexor did not demonstrate single-agent activity in RRMM.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

No. The proposed starting dose is not supported by the dose-response or exposure-response relationships for efficacy and safety.

Dose Selection Rationale

The proposed starting dose in combination with dexamethasone was selected on efficacy and safety data from Study KCP-330-001. This study included patients with RRMM which were administered selinexor doses ranging from 3 mg/m^2 to 60 mg/m^2. Details regarding the Study KCP-330-001 are provided in Section 7.2.4. As described in Section 7.2.5, most patients with MM enrolled in Study KCP-330-001 experienced stable or progressive disease. In the 45 patients with RRMM enrolled in Arm 1 (Selinexor monotherapy dose escalation), the best overall response by dose along with the duration of therapy is shown in Table 10.

Table 10: KCP-330-001 Best Overall Response by Dose in Arm 1

Best Overall Response	**Dose (mg/m^2)**										**MM (N = 45) n (%)**
	3 (N=1)	6 (N=2)	12 (N=1)	16.8 (N=5)	23 (N=6)	30 (N=2)	35 (N=13)	45 (N=10)	55 (N=1)	60 (N=4)	
ORR sCR CR PR								 **1**			**1 (2.2)** 0 (0) 0 (0) 1 (2.2)
MR				3		1	3	2		1	10 (22.2)

SD	0	2	0	1	3	1	6	1	1	2	17 (37.8)
PD	1	0	0	0	1	0	3	5	0	0	10 (22.2)
Clinical Progression			1								1 (2.2)
Not Evaluable/ Missing				1	2		1	1		1	6 (13.3)
Median Duration of therapy (range)	24	- (24,59)	24	319 (5,738)	33.5 (8,149)	- (62,123)	31 (8,409)	26.5 (3,113)	29	47.5 (10,68)	

(Source: FDA Analysis)

Selinexor in combination with 20 mg dexamethasone on days 1 and 3 of each week was evaluated in Study KCP-330-001 Schedule 6, which enrolled 25 patients with RRMM. The ORR and duration of exposure for these patients are shown in Table 11.

Table 11: KCP-330-001 Schedule 6 ORR and Median Duration of Exposure in Patients with MM

	Selinexor dose in combination with dexamethasone 20 mg on days 1 and 3 of each week in patients with RRMM (N = 25)	
	45 mg/m^2 (N = 12)	60 mg/m^2 (N = 13)
ORR, n (%)	6 (50)	0
Median duration of exposure (days) [range]	115 [8, 368]	15 [1, 93]

(Source: FDA Analysis)

As shown in Table 11, the median duration of exposure was 15 days at the selinexor 60 mg/m^2 dose due to poor tolerability and early withdrawal of consent compared to 115 days (8–365) in the selinexor 45 mg/m^2 arm with dexamethasone. The dose for Study KCP-330-012 (STORM) was selected as selinexor 80 mg in combination with 20 mg dexamethasone on Days 1 and 3 of each week without evaluation of the efficacy and safety of lower doses of selinexor below 80 mg (~45 mg/m^2) in combination with 20 mg dexamethasone.

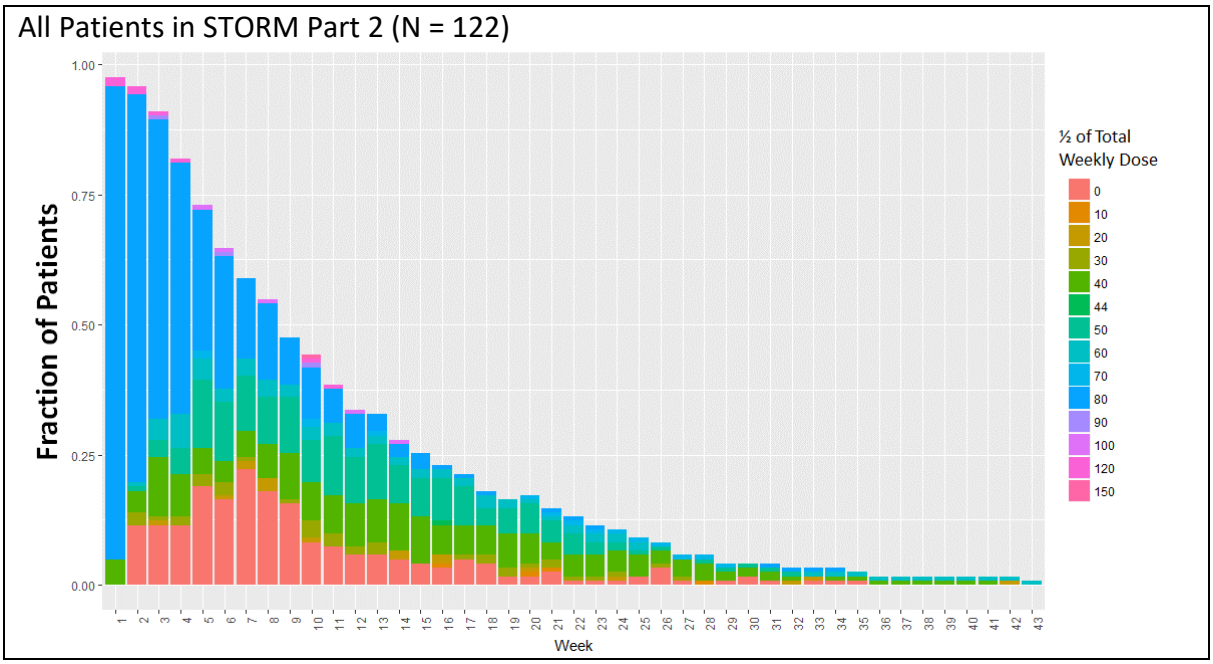
Tolerability of the Proposed Dose

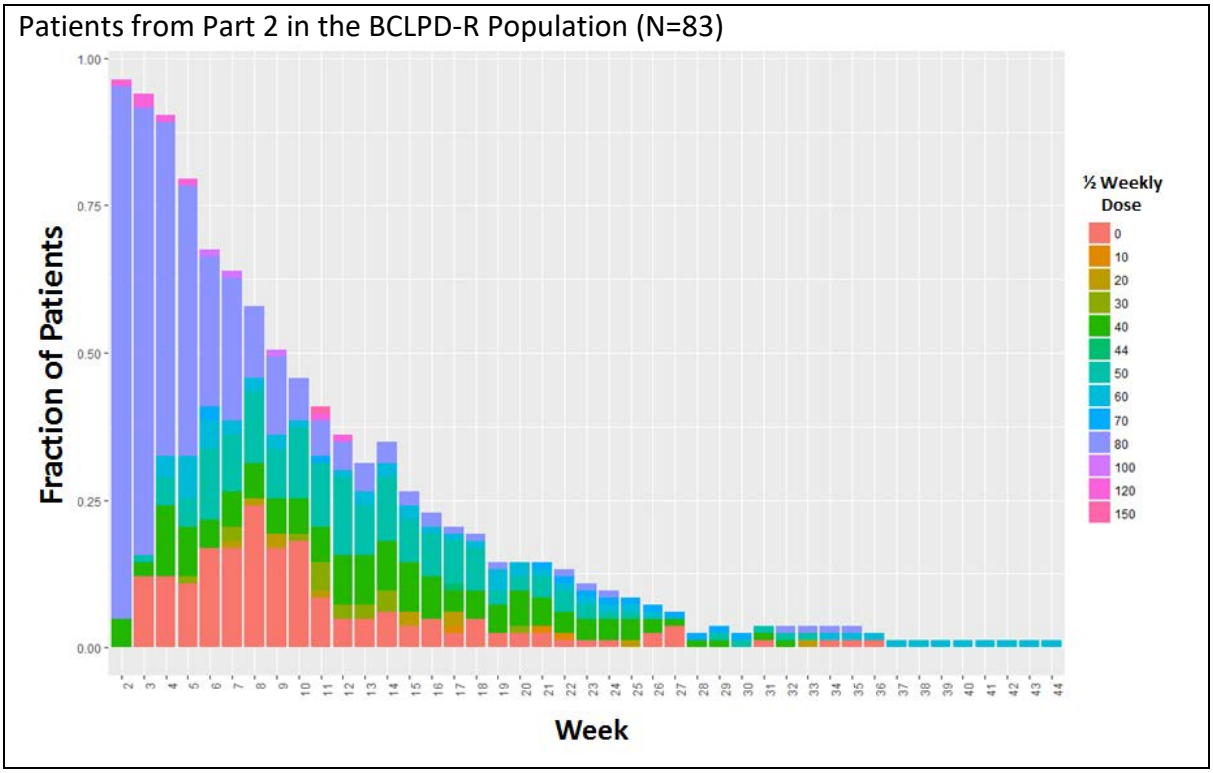
The selinexor 80 mg in combination with 20 mg dexamethasone on Days 1 and 3 of each week dose was poorly tolerated. As described in Section 7.4, the dose of selinexor 80 mg in

combination with dexamethasone 20 mg on Days 1 and 3 during Weeks 1–4 of each 28-day cycle in the STORM trial was associated with significant toxicity. This is evidenced in part, by the number of patients with at least 1 TEAE (100%), and the frequency of Grade 3–4 TEAEs (94.1%). In STORM Part 2, 91.1% of patients had a TEAE that resulted in dose modification, and 77% of patients had 2 or more dose reductions. An overview of the safety results from STORM is shown in Table 38, which summarizes the categories of treatment emergent AEs (TEAEs) observed in the trial.

The fraction of patients at each treatment level over time in Part 2 of STORM is shown in Figure 1. The treatment (dose) level is half of the total weekly dose and the figure excludes missed doses and dose-modifications due to progressive disease.

Figure 1: Selinexor Treatment Duration and Fraction of Patients at Each Selinexor Dose Level





(Source: FDA Analysis)

As shown in Figure 1, many patients either discontinued or had dose reductions early in treatment. It is important to note that the fraction of patients remaining on the starting dose continued to decrease over time, with a median duration on selinexor 80 mg twice weekly of 3.5 weeks. The occurrence of dose reductions early in therapy suggests that the starting dose may not be tolerable.

The poor tolerability of the 80 mg twice weekly with dexamethasone is consistent with that observed in the Phase 1 clinical trial (KCP-330-001) cohorts where the median (range) duration of treatment of 115 days (8–365) was observed in the selinexor 45 mg/m^2 arm twice weekly with dexamethasone.

Exposure-Response Relationships

No E-R analysis was performed for the BCLPD-R population because no PK data were available in patients in Part 2 of the STORM trial. The E-R for efficacy in Part 1 of the STORM trial was considered inconclusive due to the high dose reduction rate and limited PK data.

Exposure-response analysis for safety was performed based on pooled data from the full PK-safety set (N = 623 with PK from studies KCP-330-01, KCP-330-008, KCP-330-009, KCP-330-010, and KCP-330-012). Overall, a positive E-R relationship for safety was observed with higher selinexor exposure associated with higher incidence of adverse events such as neutropenia, thrombocytopenia, gastrointestinal disorders, vomiting, diarrhea, decreased appetite,

decreased weight, fatigue, hyponatremia, and ocular disorders. A summary of the total number and the corresponding percentage of first Grade 3 and higher adverse events in each time-averaged AUC quartile based on the full PK-safety analysis dataset is shown in Table 12.

Table 12: Grade 3 and Higher TEAEs by Selinexor Time-Averaged AUC Quartile

	Time-Averaged AUC to First Event			
Parameter	**Q1 (N = 156)**	**Q2 (N = 156)**	**Q3 (N = 156)**	**Q4 (N = 156)**
Thrombocytopenia	20 (12.8)	32 (20.5)	48 (31)	53 (34)
Neutropenia	4 (2.6)	18 (11.5)	17 (11)	27 (17.3)
Hyponatremia	3 (1.9)	8 (5.1)	16 (10.3)	33 (21.2)
Fatigue	3 (1.9)	7 (4.5)	14 (9)	13 (8.4)
GI Disorders	4 (2.6)	4 (2.6)	9 (5.8)	13 (8.4)
Decreased Appetite	3 (1.9)	3 (1.9)	5 (3.2)	8 (5.2)

(Source: FDA Analysis)

These relationships were also present for the MM patient population (N = 201 with PK, studies KCP-330-001 and KCP-330-012), indicating that lower doses may be better tolerated. The distribution of potential baseline risk factors across exposure quartiles appears to be reasonably balanced in general, except for a trend that higher exposure was associated with higher ECOG score and more prior therapies at baseline. See Appendix 13.3.3 for further analysis results and details.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No clinically significant differences effect in the PK of selinexor were observed based on age (18 to 94 years old), sex (422 male and 298 female patients), ethnicity (607 White, 46 Black, 15 Asian, 35 "Other", and 17 unknown), mild hepatic impairment (100 patients), renal impairment (277 mild, 167 moderate or 15 severe patients) in a population PK analysis.

Selinexor is mainly metabolized by oxidation and conjugation to glucuronidation and glutathione-related metabolites. The oxidation is catalyzed primarily by CYP3A4. There is no human mass balance study in this submission. The Applicant's assumption is that selinexor is excreted by the hepatobiliary route in feces with minimal excretion in urine. In human feces, the predominant metabolite observed was N-dealkylation, which is catalyzed by CYP3A4. Hepatic impairment impacts on elimination can be significant if the major excretion route is feces.

Hepatic Impairment: No clinically significant difference was observed in the apparent clearance of selinexor in patients with mild hepatic impairment (Child-Pugh class A; N= 100; Median CL/F =

16.12 L/hr) compared to patients with normal hepatic function (N=611; Median CL/F = 16.75 L/hr). As such, no dose adjustment is recommended in patients with mild hepatic impairment (Child-Pugh class A). There are limited PK data from in patients with moderate (Child-Pugh class B; N=6) or severe hepatic impairment (Child-Pugh class C; N=3) hepatic impairment in the population PK analysis. We will issue a PMR to conduct a clinical trial to determine PK of selinexor in patients with moderate and severe hepatic impairment. Refer to Post-Marketing Requirements and Commitments for details.

Renal Impairment: No clinically significant difference was observed among the apparent clearance of selinexor in patients with mild (Cockcroft-Gault estimated CLcr:60 to 89 mL/min; N=277; Median CL/F = 16.03 L/hr), moderate (Cockcroft-Gault estimated CLcr:30 to 59 mL/min; N=167; Median CL/F = 15.33 L/hr) or severe (Cockcroft-Gault estimated CLcr:15 to 29 mL/min; N=15; Median CL/F = 16.37 L/hr) renal impairment and patients with normal renal function (N=261; Median CL/F = 17.56 L/hr). As such, no dose adjustment is recommended for patients with renal impairment. The PK of selinexor in patients with end stage renal disease (Cockcroft-Gault estimated CLcr: <15 mL/min) or undergoing hemodialysis is unknown.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No clinically relevant food effect was observed with selinexor tablet TF1 formulation. In a population PK analysis, altered selinexor absorption was not identified when selinexor was co-administered with pH altering drugs (proton pump inhibitors and H2 blockers).

Selinexor is a CYP3A substrate. There is insufficient data to support the understanding of CYP3A inhibitors and inducers on selinexor exposures.

Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

To-be-marketed product (TF2.3) (b) (4) the clinical second-generation tablet formulation 2 (TF2.2 used in the registration Study KCP-330-012) except (b) (4) The applicant provided in vitro dissolution data to demonstrate BE between TF2.3 and TF2.2.

See the Biopharmaceutics review by Dr. Akm Khairuzzaman (http://panorama.fda.gov/document/view?ID=5c1cf23f0062c0036d8283bef7beee9f&activeTab=tab-document-approvals&mode=anaconda) for detail.

Wentao Fu Primary Reviewer	Olanrewaju Okusanya Team Leader
Justin C Earp Pharmacometrics Primary Reviewer	Lian Ma Pharmacometrics Team Leader

7 Statistical and Clinical Evaluation

7.1 Sources of Clinical Data and Review Strategy

7.1.1 Table of Clinical Studies

Table 13: Listing of Clinical Trials Relevant to NDA 212306

Trial	Design	Regimen	Population	Primary Endpoint
Pivotal				
KCP-330-012 (STORM) Part 2	Phase 2b, open-label, single-arm study	Selinexor 80 mg + Dex 20 mg twice weekly (Weeks 1-4)	Triple-class refractory MM (N = 123)	ORR
Supportive				
KCP-330-012 (STORM) Part 1	Phase 2b, open-label, single-arm study	Selinexor 80 mg + Dex 20 mg twice weekly (Weeks 1-3)	Triple- or double-class refractory MM (N = 79)	ORR
KCP-330-001	Phase 1, dose escalation and dose expansion study	Selinexor or Selinexor + Dex (Selinexor doses ranging from 3 mg/m^2 to 80 mg/m^2)	Advanced hematologic malignancies (N = 286; MM N=81)	Safety and tolerability
KS-50039	Retrospective, observational study using RWD	NA	Flatiron Health Analytic Database (N = 64)	OS
Additional Supportive Trials Evaluating Combination Therapy				
KCP-330-017 (STOMP)	Phase 1b/2, open-label, dose escalation and expansion study	Selinexor 60 to 100 mg once or twice weekly + various approved agents	Newly diagnosed or relapsed/refractory MM (N=117)	Safety and tolerability
KCP-330-023 (BOSTON)	Phase 3, open-label, randomized (1:1), controlled, active-comparator study	Selinexor 100 mg weekly + Bortezomib 1.3 mg/m^2 (D1, 8, 15, 22) + Dex 20 mg twice weekly vs.	Relapsed or refractory MM, 1-3 prior therapies (N = 399)	PFS

		Bortezomib + Dex per USPI		
Additional Trials Included in ISS				
KCP-330-008 (SOPRA)	Phase 2, open-label, randomized (2:1), controlled, active-comparator study	Selinexor vs. Physician Choice (BSC, BSC + LDAC, or BSC + HMA)	Relapsed or refractory AML, age ≥ 60, ineligible for transplant and/or intensive chemotherapy (N = 317)	OS
KCP-330-009 (SADAL)	Phase 2b, open-label, multiple dose cohort study	Selinexor 60 mg or 100 mg twice weekly	Relapsed/refractory DLBCL with no therapeutic options of clinical benefit	ORR
KCP-330-010	Phase 2, open-label, single-arm study	Selinexor 60 mg twice weekly	Initial or relapsed/refractory RT	ORR, DOR
KCP-330-013	Phase 2, open-label, single-arm study	Selinexor 60 mg twice weekly	Relapsed/refractory PTCL or CTCL	ORR (CR+PR)

Abbreviations: RWD = Real World Data; Dex = dexamethasone; BSC = best supportive care; LDAC = low-dose AraC; HMA = hypomethylating agent; MM = multiple myeloma; AML = acute myeloid leukemia; ORR = overall response rate; OS = overall survival; NA = not applicable; PFS = progression-free survival; DLBCL = diffuse large B-cell lymphoma; RT = Richter's transformation; PTCL = peripheral T-cell lymphoma; CTCL = cutaneous T-cell lymphoma; DOR = duration of response; USPI = US prescribing information
(Source: FDA)

7.1.2 Review Strategy

The review was primarily based on the efficacy and safety data from Part 2 of STORM. The key review materials included the following:

- NDA 212306 datasets (raw and derived), clinical study reports, and responses to the review team's information requests
- Relevant published literature
- Relevant prior regulatory history
- Applicant presentations to the FDA

The other trials listed in Table 13 were supportive trials used in the integrated analyses of safety.

Part 2 of STORM was used for the primary analysis of efficacy and safety. The Applicant submitted data sets for this study using a data cut-off date of April 24, 2018 at the time of the initial NDA submission. At the request of the FDA, the Applicant submitted updated adverse event and exposure analysis datasets (adae2.xpt and adec.xpt) for Part 2 of STORM on February 5, 2019. FDA conducted primary efficacy and safety analyses and all major efficacy and safety analyses conducted by the Applicant were reproduced or audited.

Clinical data was provided in Clinical Data Interchange Standards Consortium (CDISC) Foundational Standards SDTM and ADaM format.

Sections 7 and 8 of this review were performed jointly by Dr. Baines and Dr. Wang. Analyses by Dr. Wang were performed using SAS 9.4. Analyses by Dr. Baines were performed using JMP 12.0 (SAS Institute, Inc.). Unless specifically referenced, all analyses and presentation of findings are the work of FDA reviewers.

7.2 Review of Relevant Individual Trials Used to Support Efficacy

Analysis of efficacy is based on 122 patients comprising the modified-intent-to-treat (mITT) population enrolled in Part 2 of STORM. The primary analysis of safety includes 123 patients enrolled and treated in Part 2 of STORM. Additional safety analyses include 79 patients enrolled and treated in Part 1 of STORM, and patients with other advanced hematologic malignancies treated with selinexor in trials KCP-330-008, KCP-330-009, and KCP-330-010. The Applicant also submitted an analysis of real-world data (RWD) in support of the NDA.

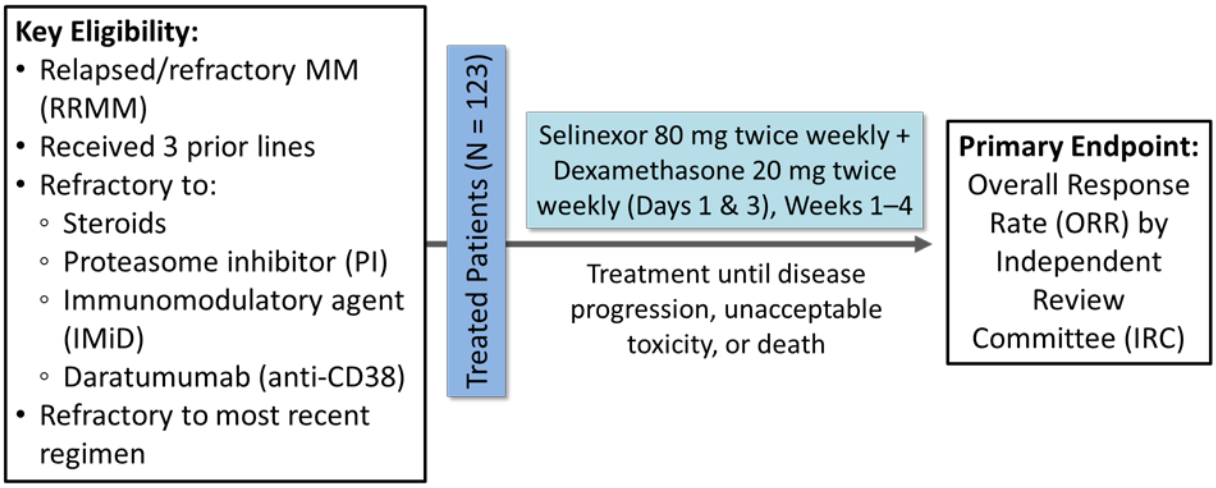
7.2.1 KCP-330-012 (STORM)

A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) Plus Low-Dose Dexamethasone in Patients with Multiple Myeloma Previously Treated with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib, and Daratumumab, and Refractory to Prior Treatment with Glucocorticoids, an Immunomodulatory Agent, a Proteasome Inhibitor, and the anti-CD38 mAb Daratumumab

Trial Design

STORM was a single-arm, open-label, multi-center, international, phase 2b trial of selinexor 80 mg twice weekly in combination with dexamethasone 20 mg twice weekly in patients with RRMM (Figure 2). Treatment was continued until disease progression, unacceptable toxicity, or death. The primary endpoint was overall response rate (ORR) as assessed by an Independent Review Committee (IRC). ORR was defined as the proportion of patients achieving at least a partial response (PR) or better (i.e., very good partial response (VGPR), complete response (CR), or stringent CR (sCR).

Figure 2: STORM Part 2 Study Design



(Source: FDA)

Trial Population and Key Eligibility Criteria

Eligible patients for STORM Part 2 were required to have received at least three prior anti-MM regimens, including an alkylating agent, lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab, and a glucocorticoid (referred to by the Applicant as "penta-exposed"). Patients also had to be refractory to prior treatment with at least one PI, at least one IMiD, and daratumumab (referred to as "triple-class refractory"), as well as glucocorticoids and their most recent anti-MM regimen. Part 2 of STORM included a subpopulation of 83 patients who were refractory to at least two PIs (i.e., bortezomib and carfilzomib), at least two IMiDs (i.e., lenalidomide and pomalidomide), and at least one anti-CD38 mAb (i.e., daratumumab), referred to as the "BCLPD-refractory" (BCLPD-R) population. Part 1 of STORM primarily

enrolled patients who were "quad-exposed" (prior treatment with lenalidomide, pomalidomide, bortezomib, carfilzomib) and "double-class refractory" (i.e., refractory to both a PI and an IMiD).

Patients were classified as refractory to a prior treatment if they met the International Myeloma Working Group (IMWG) consensus definition of relapsed and refractory MM (nonresponsive disease or progression on or within 60 days of therapy), or if they had ≤25% response to therapy. Patients were required to have measurable disease based on IMWG guidelines, however, the study also allowed patients with serum M-protein ≥0.5 g /dL (consensus criteria require serum M-protein ≥1 g/dL).

Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2. Patients with less than 4 months life expectancy were excluded. Patients with active plasma cell leukemia, systemic amyloid light chain amyloidosis, or active central nervous system MM were also excluded.

Patients had to have adequate organ function within 21 days of the start of study treatment, defined by total bilirubin <2 times the upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels <2 times ULN, and estimated creatinine clearance ≥20 mL/min by Cockcroft-Gault. Patients were also required to have adequate hematopoietic function within 21 days of the start of study treatment, defined by an absolute neutrophil count ≥1000/mm^3, platelet count ≥75,000/mm^3 (≥50,000/mm3 if >50% bone marrow plasma cells), and hemoglobin ≥8.5 g/dL.

Study Treatment

Patients in Part 2 of STORM received selinexor 80 mg (~45 mg/m^2) orally twice weekly and dexamethasone 20 mg orally twice weekly on Days 1 and 3 of Weeks 1–4 of each 28-day cycle (8 doses per cycle). In Part 1, 51 (64.6%) of the patients enrolled into an earlier version of the protocol (Version 2) were treated on an alternate schedule with twice weekly dosing of selinexor 80 mg and dexamethasone 20 mg on Weeks 1–3 of each 28-day cycle (6 doses per cycle). The remaining 28 (35.4%) patients, enrolled in Part 1 on Protocol Version 3, received 8 doses per cycle. Treatment was continued until disease progression, unacceptable toxicity, or death.

Reduction of dexamethasone to 10 mg was permitted for patients who developed partial intolerance to glucocorticoids. In select cases, selinexor could be increased to 100 mg twice weekly for patients who were tolerating treatment but had not achieved a response better than stable disease (SD), minimal response (MR) or partial response (PR).

The protocol included concomitant administration of 5-hydroxytryptamine (5-HT3) antagonists, unless contraindicated, starting on Day 1 before the first dose of selinexor, then continuing two

to three times daily as needed for nausea. Additional anti-emetics and anti-anorexic agents were recommended to be administered per National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines. Patients were permitted to receive other therapies, including blood product transfusions, antimicrobial agents, and growth factors as supportive care. Patients were also permitted to continue other baseline medications.

The protocol included dose modification guidelines for adverse events (AEs) considered related to selinexor (Table 14). The protocol also included specific guidelines for management of fatigue, anorexia, weight loss, nausea, hyponatremia, diarrhea, thrombocytopenia, anemia, and neutropenia.

Table 14: Selinexor Dose Modifications

	Dose Level	Selinexor Dosing
	1	100 mg BIW (total dose of 200 mg per week)
Starting Dose	**0**	**80 mg BIW (total of 160 mg per week)**
Dose Reductions	-1	60 mg BIW (120 mg total per week)
	-2	100 mg total per week: 100 mg one day OR divided as 60 mg and 40 mg on separate days
	-3	80 mg total per week: 80 mg one day OR divided as 40 mg per day on 2 days
	-4	60 mg total per week: 60 mg one day OR divided as 40 mg one day and 20 mg on another day
	-5	40 mg total per week: 40 mg one day OR divided as 20 mg per day on separate days

Abbreviation: BIW = twice weekly
(Source: Applicant's KCP-330-012 Protocol Version 6.0, page 59)

The Investigator could remove a patient from study treatment for any of the following reasons: disease progression according to IMWG criteria confirmed by the IRC, unacceptable AE(s) or failure to tolerate study treatment, patient decision to discontinue, or any medically appropriate reason or significant protocol violation.

Schedule of Events

Study assessments were performed at screening, during treatment, and post-treatment as outlined in Table 15.

Table 15: Schedule of Study Assessments

Activity/Assessment	Screening	Cycle 1				Cycle 2		Cycles ≥ 3	End-of-Treatment (EoT) Visit	Safety Follow-up Call	Durability of Response and Survival Follow-up[15]
	Day -21 to Day -1	Day 1	Day 3[14]	Day 8	Day 15	Day 1	Day 15	Day 1	≤ 14 Days Post Last Dose	30 Days Post-Last Dose	Every 3 mo.
		-1 day	+1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days		+ 7 days	± 14 days
Informed consent[1]	X										
Inclusion/exclusion criteria	X										
Demographics	X										
Medical history[2]	X	X									
Patient height	X										
Patient weight	X	X		X	X	X	X	X	X		
Body Surface Area (BSA)[3]	X										
Physical examination, full including vital signs[4]	X								X		
Physical examination, symptom-directed, including vital signs[4]		X		X	X	X	X	X			
ECOG[5]	X					X		X	X		
Echocardiogram or MUGA[6]	X										
12-lead ECG	X								X		
Ophthalmic exam[7]	X								X		
Clinical Labs											
Urinalysis[5]	X								X		
CBC with differential[5]	X				X	X	X	X	X		
TSH[5]	X								X		
Complete serum chemistry[5]	X					X		X	X		
Limited serum chemistry				X	X		X				
Coagulation tests[5]	X								X		
Serum hCG pregnancy test[8]	X					X (D1 of each cycle only)		X (D1 of each cycle only)	X		
C-reactive protein	X	X				X		X	X		
Multiple Myeloma Assessments											
SPEP and serum protein immunofixation[9]	X	X				X		X	X		X
UPEP (24-hr urine for total protein) and urine protein immunofixation[9]	X	X				X		X	X		X
Quantitative Ig levels[9]	X	X				X		X	X		X
Serum FLC[9]	X	X			X	X	X	X	X		X
β_2-microglobulin	X								X		
Skeletal survey[10]	X					(X)		(X)	X		(X)
Plasmacytoma assessment[11]	X					(X)		(X)	X		(X)
Bone marrow aspirate [12]	X					(X)		(X)			(X)
Bone marrow core biopsy[13]	X					(X)					
FACT-MM questionnaire	X					X		X	X		
Study drug dosing		Selinexor 80 mg + dexamethasone 20 mg (both twice weekly) for 4 weeks (each week) of 4-week cycles									
Adverse events[16]	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X		
Nutritional consultation	X										
Telephone contact[14]			X							X	X
Antineoplastic therapy after EoT									X	X	X

(Source: Applicant's KCP-330-012 Protocol Version 6.0, pages 14-15)

Study Endpoints

The primary endpoint was ORR, defined as the proportion of patients with a PR or better. Key secondary endpoints included duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Responses were assessed by an IRC based on the IMWG 2016 response criteria (Kumar S, 2016). Two consecutive samples were required to confirm a response.

Assessment of Health-related Quality of Life (HR-QoL) using the Functional Assessment of Cancer Therapy–Multiple Myeloma (FACT-MM) questionnaire, was included as a secondary efficacy endpoint. The FACT-MM questionnaire included the general FACT Physical Well-Being (7 items), Social/Family Well-Being (7 items), Emotional Well-Being (6 items), and Functional Well-Being (7 items) subscales combined with a 14-item MM-specific subscale, for a total trial outcomes index (TOI) of 41 items with a TOI score ranging from 0 to 120. The assessment was performed at baseline, Day 1 of each cycle starting from Cycle 2, and at the final study visit.

Statistical Analysis Plan

The data cut-off date for analysis of STORM was April 24, 2018. The first patient was enrolled on May 26, 2015, and the last patient was enrolled on March 23, 2018.

Disease response in Part 2 of STORM was assessed per the IMWG 2016 criteria and adjudicated by an IRC. A portion of the responses in Part 1 were assessed per IMWG 2014 criteria (Rajkumar SV, 2014). Laboratory evaluations for MM disease parameters were performed at the start of each treatment cycle.

The primary efficacy endpoint was ORR by IRC assessment, defined as the proportion of patients achieving sCR, CR, VGPR, or PR. Key secondary endpoints included DOR, clinical benefit rate (CBR), disease control rate (DCR), PFS, OS, time-to-progression (TTP) and quality of life (QoL) using the FACT-MM instrument. It was estimated that a sample size of 122 patients for Part 2 would yield 90% power to detect an ORR of ≥20% against a minimal threshold of 10%, using a one-sided test with α=0.025. The mITT population was defined as patients in Part 2 who met all eligibility criteria (or received a waiver to participate) and received at least one dose of selinexor.

Protocol Amendments

The original protocol (Version 1) was dated December 24, 2014. The protocol was amended 6 times, with the most recent version (Version 6) dated December 13, 2017.

Key protocol revisions include the following:

- Amendment 1 (Version 2, dated February 5, 2015): Added clarification that endpoints of PFS, QoL, and OS would not be tested for statistical significance in response to the FDA comment that time-to-event endpoints are not evaluable in non-controlled trials

- Amendment 2 (Version 3, dated September 25, 2015): Revised study population from patients with MM refractory to lenalidomide, pomalidomide, bortezomib, and carfilzomib ("quad-refractory) to patients with MM exposed to lenalidomide, pomalidomide, bortezomib, and carfilzomib and double-refractory to both a PI and an IMiD; changed study treatment dose schedule from twice weekly for 3 out of a every 4 weeks to twice weekly for each week of a 4-week cycle
- Amendment 3 (Version 4, dated August 11, 2016): Revised to enroll approximately 130 additional patients to expand the population of patients with "penta-refractory" MM; indication revised to MM previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and an anti-CD38 monoclonal antibody (mAb) (i.e., daratumumab or isatuximab) and refractory to prior treatment with glucocorticoids, an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and an anti-CD38 mAb; revised definition of the mITT population for primary efficacy analysis to include Part 2 patients with "penta-refractory" MM who meet all eligibility criteria and receive at least one dose of study treatment
- Amendment 4 (Version 5, dated April 28, 2017): Revised eligibility criteria to remove isatuximab as an allowable anti-CD38 agent for inclusion in the study

Data Quality and Integrity: Sponsor's Assurance

The Applicant submitted this NDA, including the clinical study report and data files for study KCP-330-012, to the FDA CDER Electronic Document Room (EDR). The data in this submission are in Electronic Common Technical Document (eCTD) format, in accordance with FDA guidance on electronic submissions. Define files were included for the datasets.

7.2.2 Study Results

Compliance with Good Clinical Practices

The Applicant provided attestation that this study was conducted in accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Council for Harmonization (ICH) guidelines on Good Clinical Practice (GCP), and regulatory requirements as applicable.

Financial Disclosure

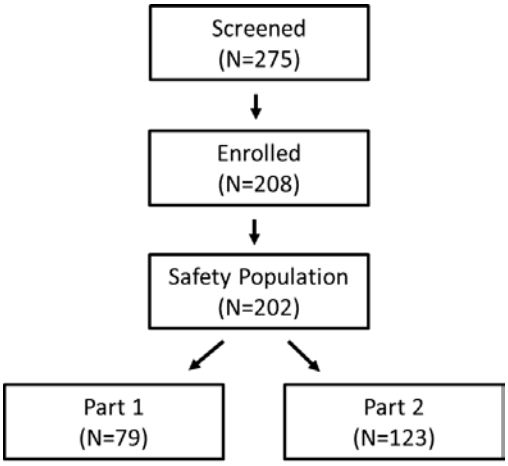
The Applicant stated that information regarding financial disclosures was obtained from all Investigators. Financial disclosure forms were not completed for 5 sub-Investigators at site (b) (6) however, the Applicant stated that the site confirmed these individuals did not have any disclosable interests. One Investigator at site (b) (6) was removed from the Form FDA 1572 prior to the study being approved and did not participate in the trial, therefore no financial disclosure form was collected. One Investigator at site (b) (6) was listed on Form FDA 1572 in error, and therefore a financial disclosure form was not collected.

Reviewer Comment: None of these issues are anticipated to affect the integrity of the trial.

Patient Disposition

In total, 275 patients were screened, and 208 patients were enrolled. Reasons for screen failures were not included in the dataset. The first patient was enrolled on May 26, 2015 and the last patient was enrolled on March 23, 2018. Of the 208 patients who enrolled, 202 received at least one dose of selinexor (Figure 3). A total of 79 patients were treated in Part 1 of STORM, and 123 patients were treated in Part 2 of STORM.

Figure 3: STORM Disposition



(Source: FDA)

As of the April 24, 2018 data cut-off date, of the 123 patients treated in Part 2 of STORM, 17 (13.8%) remained on treatment, 106 (86.2%) had discontinued treatment, and 42 (34.1%) remained in follow-up (Table 16).

Table 16: STORM Disposition

Study Disposition	**Part 1 (N = 79) n (%)**	**Part 2 (N = 123) n (%)**	**Total (N = 202) N (%)**
On Treatment	0	17 (13.8)	17 (8.4)
Discontinued Treatment	79 (100)	106 (86.2)	185 (91.6)
Reason for Discontinuation			
Disease Progression	45 (57)	59 (48)	104 (51.5)

Adverse Event	18 (22.8)	31 (25.2)	49 (24.3)
Withdrawal/Lost to Follow-up	6 (7.6)	7 (5.7)	13 (6.4)
Physician Decision	8 (10.1)	4 (3.3)	12 (5.9)
Other	1 (1.3)	3 (2.4)	4 (2)
Death	1 (1.3)	2 (1.6)	3 (1.5)

(Source: FDA Analysis)

Protocol Violations/Deviations

Protocol deviations were categorized as minor or major (potentially impacting patient safety or key safety and efficacy analyses). The Applicant identified 17 major protocol deviations in Part 1 of STORM and 30 major protocol deviations in Part 2 of STORM (47 in total). Details of the protocol deviations are summarized in Table 17.

Reviewer Comment: One patient in Part 2 who did not receive prior carfilzomib was not included in the mITT population.

Table 17: STORM Protocol Deviations

Protocol Deviations	**Part 1 (N = 79) n (%)**	**Part 2 (N = 123) n (%)**	**Total (N = 202) N (%)**
Major Protocol Deviations	17 (21.5)	30 (24.4)	47 (23.3)
Category of Major Protocol Deviations			
Dosing Errors*	1 (1.3)	13 (10.6)	14 (6.9)
Eligibility Criteria	10 (12.7)	5 (4.1)	15 (7.4)
Informed Consent Form	5 (6.3)	8 (6.5)	13 (6.4)
Adverse Event Reporting	1 (1.3)	4 (3.3)	5 (2.5)

*Includes patients with dosing errors/non-compliance, or patients who continued to receive selinexor after experiencing disease progression/being off therapy >28 days
(Source: Applicant's KCP-330-012 Clinical Study Report, page 78)

Table of Demographic Characteristics

The baseline characteristics of patients enrolled and treated on STORM are shown in Table 18.

Table 18: Demographics of Patients in STORM

Demographic Variable	**Part 1 (N = 79) n (%)**	**Part 2 (N = 123) n (%)**	**Total (N = 202) n (%)**
Sex			
Male	37 (46.8)	71 (57.7)	108 (53.5)
Female	42 (53.1)	52 (42.3)	94 (46.5)
Age			
Median (range)	63 (34 – 78)	65 (40 – 85)	64 (34 – 85)
40-64	44 (55.7)	60 (48.8)	104 (51.5)
>65	34 (4)	63 (51.2)	97 (48)
Race			
Missing	1 (1.3)	5 (4.1)	6 (3)
Asian	0	2 (1.6)	2 (1)
Black/African American	14 (17.7)	21 (17.1)	35 (17.3)
Hawaiian/Pacific Islander	0	1 (0.8)	1 (0.5)
Other	2 (2.5)	8 (6.5)	10 (5)
White	62 (78.5)	86 (69.9)	148 (73.3)

(Source: FDA Analysis)

Reviewer Comment: The median age of patients enrolled in STORM with RRMM was 64, which is younger than the median age at diagnosis of 69 for patients with NDMM in the U.S. Otherwise, the demographic characteristics of patients in STORM were similar to the U.S. population of patients with MM.

All 20 study sites for Part 1 of STORM were in the U.S. Part 2 enrolled 84 (68.3%) patients at 20 U.S. sites, 1 (0.8%) patient in Austria, 7 (5.7%) patients at 4 sites in Belgium, 10 (8.1%) patients at 5 sites in Germany, 14 (11.4%) patients at 7 sites in France, and 7 (5.7%) patients at 1 site in Greece.

Other Baseline Characteristics (e.g., disease characteristics, prior therapies)

Table 19 summarizes the baseline disease characteristics for patients enrolled in STORM. Most patients had an ECOG performance status score of 0–1. Nearly one-third of the patients had

International Staging System (ISS) stage 3 disease; however, ISS stage at diagnosis was missing for approximately one-third of the patients. Approximately two-thirds of patients had <50% plasma cells at diagnosis. Approximately 62% of patients had IgG subtype MM, 17% of patients had IgA subtype MM, 1 patient had IgD subtype MM, and 15% of patients had light chain only MM, consistent with the distribution of these subtypes in the general population of patients with MM. Almost all patients (96.5%) had information regarding cytogenetic abnormalities available from FISH testing. The trial included patients with high-risk cytogenetic features, including del(17p), t(4:14), t(14;16) and gain(1q21).

Table 19 Baseline Disease Characteristics of Patients in STORM

	Part 1 (N = 79) n (%)	**Part 2 (N = 123) n (%)**	**Total (N = 202) n (%)**
ECOG Score			
Missing	6 (7.6)	3 (2.4)	9 (4.5)
0	15 (19)	37 (30.1)	52 (25.7)
1	49 (62)	72 (58.5)	121 (60)
2	9 (11.4)	11 (8.9)	20 (9.9)
ISS Stage at Diagnosis			
Missing	20 (25.3)	41 (33.3)	61 (30.2)
I	19 (24.1)	21 (17.1)	40 (19.8)
II	13 (16.5)	23 (18.7)	36 (17.8)
III	27 (34.2)	38 (30.9)	65 (32.2)
Plasma Cell %			
Missing	4 (5.1)	15 (12.2)	19 (9.4)
<50%	48 (60.8)	80 (65)	128 (63.4)
≥50%	27 (34.2)	28 (22.8)	55 (27.2)
Immunoglobulin Subtype			
IgA	17 (21.5)	18 (14.6)	35 (17.3)
IgG	47 (59.5)	78 (63.4)	125 (61.9)
IgD	1 (1.3)	0	1 (0.5)

Unknown	14 (17.7)	27 (22)	41 (20.3)
Free light chain only	9 (11.4)	22 (17.9)	31 (15.3)
Cytogenetics			
FISH Performed	78 (98.7)	117 (95.1)	195 (96.5)
del(17p)	41 (51.8)	32 (26)	73 (36.1)
t(4;14)	21 (26.6)	17 (13.8)	38 (18.8)
t(14;16)	6 (7.6)	5 (4.1)	11 (5.4)
1q21	32 (40.5)	40 (32.5)	72 (35.6)
del(13)	26 (32.9)	25 (20.3)	51 (25.2)

(Source: FDA Analysis)

Table 20 summarizes the prior therapies for patients in STORM. In general, STORM enrolled patients with heavily pre-treated MM, with a median of 7 and range of 2–18 prior lines of therapy. The range for patients enrolled in Part 2 was 3–18 prior lines, consistent with the eligibility criteria for Part 2, which required at least 3 prior lines of therapy. A total of 122 of 123 patients in Part 2 had triple-class refractory MM and had received prior bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab. One patient in Part 2 was excluded from the mITT population for the primary efficacy analysis because they did not receive prior carfilzomib. Part 1 enrolled 31 (39.2%) patients who had triple-class refractory MM and had received prior bortezomib, carfilzomib, lenalidomide, pomalidomide and an anti-CD38 mAb; however, 11 of these patients had received prior isatuximab (an investigational anti-CD38 mAb) rather than daratumumab.

Table 20: Prior Therapies for Patients in STORM

	Part 1 (N = 79) n (%)	**Part 2 (N = 123) n (%)**	**Total (N = 202) n (%)**
Prior Lines of Therapy			
2	1 (1.3)	0	1 (0.5)
3	2 (2.5)	3 (2.4)	5 (2.5)
4	4 (5.1)	12 (9.8)	16 (7.9)
5	9 (11.4)	14 (11.4)	23 (11.4)
6	15 (19)	22 (17.9)	37 (18.3)
7	14 (17.7)	16 (13)	30 (14.9)
8	12 (15.2)	20 (16.3)	32 (15.8)

9 ≥10	4 (5.1) 18 (22.8)	5 (4.1) 31 (25.2)	9 (4.5) 49 (24.3)
Median Prior # Therapies (Range)	7 (2–18)	7 (3–18)	7 (2–18)
Prior Bortezomib, Carfilzomib, Lenalidomide, Pomalidomide, and Daratumumab	20 (25.3)	122 (99.2) †	142 (70.3)
Double-Class Refractory	76 (96.2)	123 (100)	199 (98.5)
Triple-Class Refractory	31 (39.2) *	123 (100)	154 (76.2)
Response to Last Therapy			
Missing PD SD MR ≥PR	7 (8.9) 32 (40.5) 17 (21.5) 9 (11.4) 14 (17.7)	15 (12.2) 16 (13) 30 (24.4) 10 (8.1) 52 (42.3)	22 (10.9) 48 (23.8) 47 (23.3) 19 (9.4) 66 (32.7)
Prior Daratumumab In Last Line of Therapy As Monotherapy As Combination Therapy	21 (26.6) 12 (15.2) 14 (17.7) 7 (8.9)	123 (100) 58 (47.2) 36 (29.3) 87 (70.7)	144 (71.3) 70 (34.7) 50 (24.8) 94 (46.5)
Stem Cell Transplantation	67 (84.8)	102 (82.9)	169 (83.7)
Checkpoint Inhibitor	1 (1.3)	19 (15.4)	20 (9.9)

† One patient in Part 2 did not receive prior carfilzomib.
* Includes patients refractory to daratumumab and/or isatuximab (anti-CD38 mAb).
(Source: FDA Analysis)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was assessed at each study visit via tablet count. The Applicant stated that 100% of the mITT population in STORM Part 2 received ≥70% of their assigned doses of selinexor and dexamethasone.

Efficacy Results – Primary Endpoint

The mITT population was the primary efficacy analysis population. It included 122 patients with triple-class refractory MM enrolled in Part 2 of STORM who met all eligibility criteria and received at least one dose of selinexor and dexamethasone. The ORR was assessed by an IRC and results were compared to a minimal threshold of 10%. The analysis used a 2-sided, exact 95% confidence interval (CI), calculated for the rate of ORR among the mITT population. DOR was a key secondary endpoint, with the median DOR and 95% CI estimated based on the

Kaplan-Meier method. The results of the primary and key secondary efficacy analyses are summarized in Table 21. The ORR was 25.4% (95% CI: 18%, 34.1%), and the median DOR was 4.4 months (range 0.8 to 9.0 months). Responses included 2 patients with sCR, 6 patients with VGPR, and 23 patients with PR.

Table 21: Primary Efficacy Results for mITT Population in STORM Part 2

IRC Assessment	
mITT Population (N = 122)	
ORR (≥ PR), n (%); [95% CI] sCR CR VGPR PR	31 (25.4); [18, 34.1] 2 (1.6); [0.2, 5.8] 0 6 (4.9); [1.8, 10.4] 23 (18.9); [12.3, 26.9]
Responders (N = 31)	
DOR, median; [range]	4.4 months; [0.8, 9 months]

Abbreviations: IRC = Independent Review Committee; mITT = modified intent-to-treat; ORR = overall response rate; sCR = stringent complete response; CR = complete response; VGPR = very good partial response; PR = partial response; DOR = duration of response
(Source: FDA Analysis)

Reviewer Comment: An ORR of 25.4% is a modest response rate for this population and the duration of response was limited at only 4.4 months. It is unclear whether this represents a substantially meaningful clinical benefit in this population considering the degree of toxicity associated with treatment with selinexor.

Table 22 shows the ORR for subgroups (gender, age group and region) for Part 2 (mITT population) of STORM by IRC assessment.

Table 22: Subgroup Analysis of ORR for mITT Population in STORM Part 2

Subgroup (N = 122)	**ORR, n (%); [95% CI]**
Gender	
Male (N = 71)	15 (21.1); [12.3, 32.4]
Female (N = 51)	16 (31.4); [19.1, 45.9]
Age	
18-64 years (N = 60)	15 (25); [14.7, 37.9]

65-74 years (N = 44)	11 (25); [13.2, 40.3]
≥ 75 years (N = 18)	5 (27.8); [9.7, 53.5]
Race	
Missing (N = 5)	1 (20); [0.1, 71.6]
Asian (N = 2)	1 (50) [1.3, 98.7]
Black/African American (N = 21)	7 (33.3); [14.6, 57]
Hawaiian/Pacific Islander (N = 1)	0
Other (N = 8)	2 (25) [3.2, 65.1]
White (N = 85)	20 (23.5); [15, 34]
Region	
US (N = 84)	26 (31); [21.3, 42]
Non-US (N = 38)	5 (13.2); [4.4, 28.1]
MM Disease Subtype	
Free light chain only (N = 20)	9 (45); [23.1, 68.5]

(Source: FDA Analysis)

Reviewer Comment: Subgroup analysis is limited by the small numbers of patients in each subgroup; however, there were no significant differences in response based on gender, age, or race. There was a trend towards lower response rate in patients treated at sites outside of the U.S., however, the number of patients treated outside of the U.S. is much smaller, and the 95% confidence levels for U.S. vs. Non-U.S. are overlapping. There was a trend towards increased response rate in patients with free light chain-only MM; however, the numbers of patients with free light chain-only disease in Part 2 were small (17.9%). It is unclear from a clinical/biological perspective why a higher response rate would occur in patients with free light chain-only MM.

Data Quality and Integrity

The quality of the submitted data was adequate to allow substantial primary review.

Efficacy Results – Secondary and other relevant endpoints

Dose/Dose Response

Refer to the Clinical Pharmacology section for further details on dose and dose response.

Durability of Response

The median DOR was 4.4 months (Table 21).

Reviewer Comment: The limited duration of response of 4.4 months is acceptable in this population of patients with RRMM.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

In STORM, HR-QoL was assessed at baseline, on Day 1 of each cycle from Cycle 2 onward, and at the End-of-Treatment visit, using the FACT-MM questionnaire.

The Applicant reported that overall, study treatment led to median decreases of -1 to -2 from baseline in the FACT-MM TOI score from Cycle 3 Day 1 to Cycle 6 Day 1.

Table 23 shows the FACT-MM completion rates for the mITT and overall study population at baseline and by cycle from Cycles 2-6 (Day 1 of each cycle).

Table 23: FACT-MM Completion Rates by Cycle

Study Visit	**mITT (N = 122) n (%)**	**Overall (N = 202) n (%)**
Baseline	107 (87.7)	172 (85.1)
Cycle 2	69 (56.6)	110 (54.5)
Cycle 3	36 (29.5)	61 (30.2)
Cycle 4	22 (18)	40 (19.8)
Cycle 5	13 (10.7)	26 (12.9)
Cycle 6	10 (8.2)	16 (7.9)

(Source: FDA Analysis)

Reviewer Comment: It is extremely challenging to interpret PRO data in an open-label single arm trial. Moreover, the data reported is limited in scope given the high attrition rate early in the trial. By Cycle 3, less than one-third of patients had FACT-MM scores available, and by Cycle 6, less than 10% of patients had scores available.

7.2.3 Updated Efficacy Results following Major Amendment

The revised mITT population proposed as part of the major amendment consisted of a subpopulation of 83 patients with RRMM from Part 2 of STORM who received at least four prior therapies and whose disease was refractory to at least two PIs, at least two IMiDs, and an anti-

CD38 mAb. This subgroup is referred to as the BCLPD-R population.

Table of Demographic Characteristics

Demographic characteristics of the BCLPD-R subgroup (a subset of patients enrolled in STORM Part 2) are shown in comparison to the overall population in STORM in Table 24.

Table 24: Demographic Characteristics of BCLPD-Refractory Patients

Demographic Variable	**BCLPD-R (N = 83) n (%)**	**Total (N = 202) n (%)**
Sex		
Male	51 (61.4)	108 (53.5)
Female	32 (38.6)	94 (46.5)
Age		
Median (range)	65 (40 – 85)	64 (34 – 85)
40-64	40 (48.2)	104 (51.5)
>65	43 (51.8)	97 (48)
Race		
Missing	3 (3.6)	6 (3)
Asian	2 (2.4)	2 (1)
Black/African American	13 (15.7)	35 (17.3)
Hawaiian/Pacific Islander	1 (1.2)	1 (0.5)
Other	6 (7.2)	10 (5)
White	58 (69.9)	148 (73.3)

(Source: FDA Analysis)

Reviewer Comment: The demographic characteristics of the BCLPD-R subgroup did not differ substantially from the patients in Part 2 or the overall population in STORM.

Other Baseline Characteristics (e.g., disease characteristics, prior therapies)

Baseline disease characteristics of the BCLPD-R subgroup are shown in comparison to the overall population in STORM in Table 25.

Table 25: Baseline Disease Characteristics of BCLPD-Refractory Patients

	BCLPD-R (N = 83) n (%)	**Total (N = 202) n (%)**
ECOG Score		
Missing	2 (2.4)	9 (4.5)
0	27 (32.5)	52 (25.7)
1	47 (56.6)	121 (60)
2	7 (8.4)	20 (9.9)
ISS Stage at Diagnosis		
Missing	34 (41)	61 (30.2)
I	12 (14.5)	40 (19.8)
II	15 (18.1)	36 (17.8)
III	22 (26.5)	65 (32.2)
Plasma Cell %		
Missing	10 (12)	19 (9.4)
<50%	53 (63.9)	128 (63.4)
≥50%	20 (24.1)	55 (27.2)
Immunoglobulin Subtype		
IgA	14 (16.9)	35 (17.3)
IgG	53 (63.9)	125 (61.9)
IgD	0	1 (0.5)
Unknown	16 (19.3)	41 (20.3)
Cytogenetics		
FISH Performed	80 (96.4)	195 (96.5)
del(17p)	27 (32.5)	73 (36.1)

t(4;14)	12 (14.5)	38 (18.8)
t(14;16)	4 (4.8)	11 (5.4)
1q21	27 (32.5)	72 (35.6)
del(13)	15 (18.1)	51 (25.2)

(Source: FDA Analysis)

Details of prior therapies received by patients in the BCLPD-R subgroup are shown in Table 26. Patients in the BCLPD-R subgroup received a median of 8 prior therapies (range 4 – 18) compared to a median of 7 prior therapies (range 2 – 18) in the overall STORM population. By definition, patients in the BCLPD-R subgroup were refractory to at least two PIs (bortezomib and carfilzomib), at least two IMiDs (lenalidomide and pomalidomide) and an anti-CD38 mAb (daratumumab).

Table 26: Prior Therapies for BCLPD-Refractory Patients

	BCLPD-R (N = 83) n (%)	**Total (N = 202) n (%)**
Prior Lines of Therapy		
2 3 4 5 6 7 8 9 ≥10	0 0 4 (4.8) 11 (13.3) 11 (13.3) 12 (14.5) 15 (18.1) 5 (6) 25 (30)	1 (0.5) 5 (2.5) 16 (7.9) 23 (11.4) 37 (18.3) 30 (14.9) 32 (15.8) 9 (4.5) 49 (24.3)
Median Prior # Therapies (Range)	8 (4 – 18)	7 (2 – 18)
Prior Bortezomib, Carfilzomib, Lenalidomide, Pomalidomide, and Daratumumab	83 (100)	142 (70.3)
Double-Class Refractory	83 (100)	199 (98.5)
Triple-Class Refractory	83 (100)	154 (76.2)
BCLPD-Refractory	83 (100)	83 (41.1)
Response to Last Therapy		

Missing PD SD MR ≥PR	11 (13.3) 14 (16.9) 20 (24.1) 7 (8.4) 31 (37.3)	22 (10.9) 48 (23.8) 47 (23.3) 19 (9.4) 66 (32.7)
Prior Daratumumab In Last Line of Therapy As Monotherapy As Combination Therapy	83 (100) 36 (43.4) 26 (31.3) 57 (68.7)	144 (71.3) 70 (34.7) 50 (24.8) 94 (46.5)
Stem Cell Transplantation	67 (80.7)	169 (83.7)
Checkpoint Inhibitor	13 (15.7)	20 (9.9)

(Source: FDA Analysis)

Reviewer Comment: Patients in the BCLPD-R subgroup received a minimum of four prior therapies compared to a minimum of two prior therapies in STORM overall. Consistent with being a more heavily pre-treated population, more patients in the BCLPD-R subgroup received daratumumab as combination therapy (68.7% vs. 46.5%) and had prior treatment with a checkpoint inhibitor (15.7% vs. 9.9%).

Efficacy Results – Primary Endpoint

The results of the revised primary and key secondary efficacy analyses are summarized in Table 27. The ORR was 25.3% (95% CI: 16.4%, 36%) and the mDOR was 3.8 months (range 0.7, 8.1 months). Responses included 1 patient with sCR, 4 patients with VGPR, and 16 patients with PR.

Table 27 Primary Efficacy Results for BCLPD-Refractory mITT Population

IRC Assessment	
BCLPD-Refractory mITT Population (N = 83)	
ORR (≥ PR), n (%); [95% CI] sCR CR VGPR PR	21 (25.3); [16.4, 36] 1 (1.2); [0, 6.5] 0 4 (4.9); [1.3, 11.9] 16 (19.5); [11.4, 29.4]
Responders (N = 21)	
DOR, median; [range]	3.8 months; [0.7, 8.1 months]

Abbreviations: IRC = Independent Review Committee; mITT = modified intent-to-treat; ORR = overall response

rate; sCR = stringent complete response; CR = complete response; VGPR = very good partial response; PR = partial response; DOR = duration of response; BCLPD = bortezomib-, carfilzomib-, lenalidomide-, pomalidomide-, daratumumab-refractory
(Source: FDA Analysis)

ORR results for the BCLPD-R population by important subgroups are summarized in Table 28.

Table 28 Subgroup Analysis of ORR for BCLPD-R mITT Population

Subgroup (N = 83)	**ORR, n (%); [95% CI]**
Gender	
Male (N = 51)	12 (23.5); [12.8, 37.5]
Female (N = 32)	9 (28.1); [13.8, 46.8]
Age	
18-64 years (N = 40)	10 (25); [12.7, 41.2]
65-74 years (N = 31)	7 (22.6); [9.6, 41.1]
≥ 75 years (N = 12)	4 (33.3); [9.9, 65.1]
Race	
Missing (N = 3)	1 (33.3); [0.8, 90.6]
Asian (N = 2)	1 (50); [1.3, 98.7]
Black/African American (N = 13)	3 (23.1); [5, 53.8]
Hawaiian/Pacific Islander (N = 1)	0
Other (N = 6)	1 (16.7); [0.4, 64.1]
White (N = 58)	15 (25.9); [15.3, 39]
Region	
US (N = 58)	17 (29.3); [18.1, 42.7]
Non-US (N = 25)	4 (16); [4.5, 36.1]
MM Disease Subtype	
Free light chain only (N = 13)	6 (46.2); [19.2, 74.9]

Abbreviations: IRC = Independent Review Committee; mITT = modified intent-to-treat; ORR = overall response rate; BCLPD = bortezomib-, carfilzomib-, lenalidomide-, pomalidomide-, daratumumab-refractory
(Source: FDA Analysis)

Reviewer Comment: As for the mITT analysis, subgroup analysis of the BCLPD-R subpopulation is limited by the small numbers of patients in each subgroup; however, there were no significant differences in response based on gender, age, or race. As with the full mITT population, there was a trend towards lower response rate in patients treated at sites outside of the U.S. and a trend towards increased response rate in patients with free light chain-only MM; however, the numbers of patients are small, and the 95% confidence intervals are overlapping.

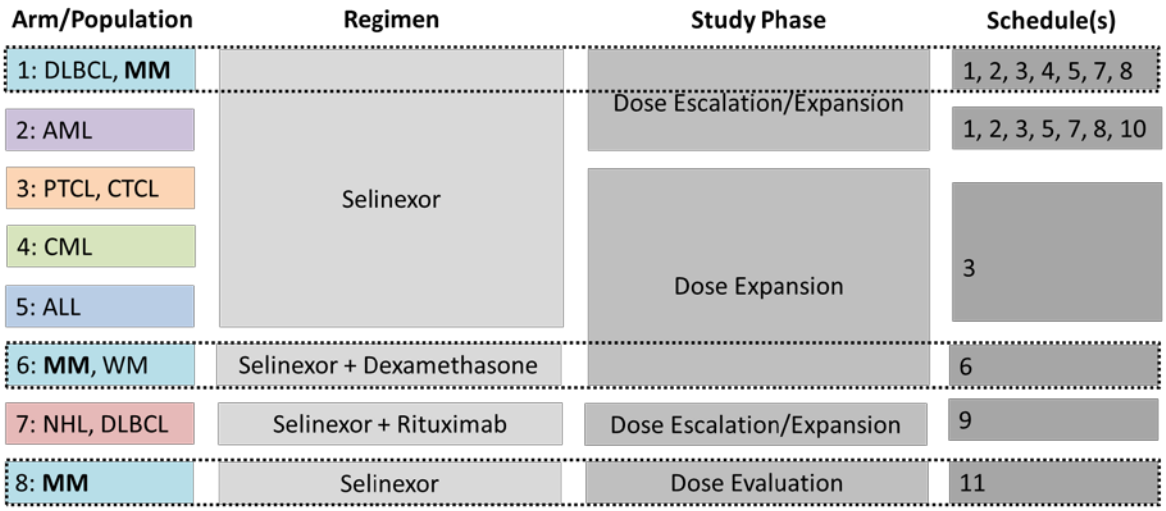
7.2.4 KCP-330-001

A Phase I Study of the Safety, Pharmacokinetics and Pharmacodynamics of Escalating Doses of the Selective Inhibitor of Nuclear Export/SINE Compound KPT-330 in Patients with Advanced Hematological Malignancies

Trial Design

KCP-330-001 was an open-label, multi-center, phase 1 dose escalation and dose expansion trial to evaluate the safety, PK, and PD of selinexor in patients with advanced hematologic malignancies. The trial included 8 arms and 11 different dose schedules (Figure 4).

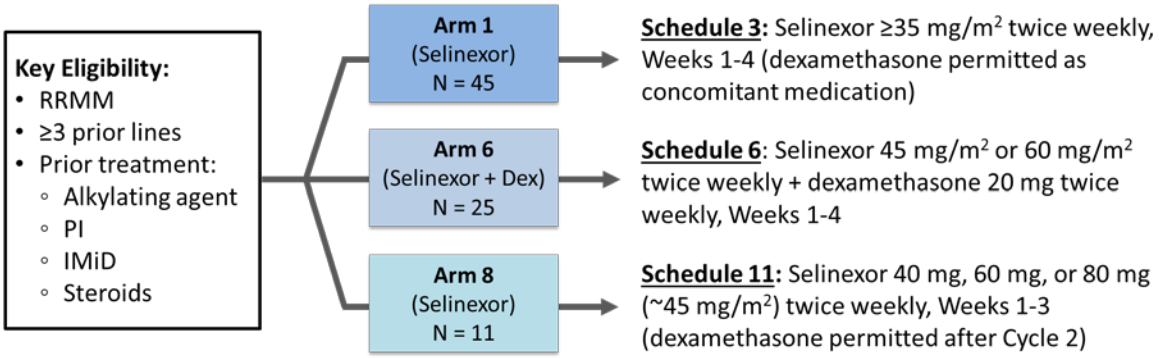
Figure 4: KCP-330-001 Trial Design



Abbreviations: DLBCL = diffuse large B-cell lymphoma; PTCL = peripheral T-cell lymphoma; CTCL = cutaneous T-cell lymphoma; CML = chronic myelogenous leukemia; ALL = acute lymphoblastic leukemia; WM = Waldenström's macroglobulinemia; NHL = non-Hodgkin's lymphoma
(Source: FDA)

Arms 1, 6, and 8 included patients with MM (Figure 5). Patients on Arms 1 and 8 received selinexor monotherapy, and patients on Arm 6 received selinexor in combination with dexamethasone. Patients on Schedule 11 (Arm 8) were permitted to receive dexamethasone as a concomitant medication after Cycle 2.

Figure 5: KCP-330-001 MM Cohorts



(Source: FDA)

Trial Population and Key Eligibility Criteria

To be eligible for KCP-330-001, patients with hematologic malignancies had to be refractory to or intolerant of established therapies known to provide clinical benefit for their condition. All patients were required to have evidence of progressive disease on study entry.

Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 1. Patients had to have adequate organ function within 14 days of the start of study treatment, defined by total bilirubin <2 times the upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels <2.5 times ULN, and estimated creatinine clearance ≥30 mL/min by Cockcroft-Gault.

For Arms 1, 3, 6, 7, and 8, patients were also required to have adequate hematopoietic function within 14 days of the start of study treatment, defined by a total white blood cell count ≥1500/mm^3, an absolute neutrophil count ≥800/mm^3 (independent of growth factor support), platelet count ≥30,000/mm^3, and hemoglobin ≥8 g/dL.

Eligible patients for the MM cohorts of KCP-330-001 were required to have had at least 3 prior lines of therapy, including an alkylating agent, a PI, an IMiD, and steroids. Patients had to have symptomatic and measurable disease based on at least one of the following criteria: (a) serum M-protein ≥0.5 g/dL, (b) urinary M-protein ≥200 mg/24 hours, or (c) abnormal serum free light chain ratio with involved light chain ≥10 mg/dL. Patients who required glucocorticoids for other comorbidities were excluded from Arm 8.

Study Treatment

Study treatment on Arm 1 during the dose escalation phase followed a standard 3+3 design with a starting dose of selinexor 3 mg/m^2. During the dose expansion phase, Arm 1 followed

Schedule 3 and Arm 6 followed Schedule 6. The dose evaluation cohort (Arm 8) followed Schedule 11 (Figure 5, above).

Study Objectives

The primary objectives of the study were to evaluate the safety and tolerability of selinexor and determine the recommended phase 2 dose (RP2D) of selinexor for patients with hematological malignancies. Secondary objectives of the study included assessment of PK and PD, evaluation of preliminary anti-tumor activity, confirmation of the RP2D in the expansion portion of the study, assessment of OS, and comparison of three dose levels of selinexor without dexamethasone in patients with MM (Arm 8).

Statistical Analysis Plan

The maximum tolerated dose was defined as the dose one level below the dose at which >1 of 3 or ≥2 of 6 patients experiences a dose-limiting toxicity (DLT). Safety and tolerability were evaluated based on DLTs, AE reports, physical exams, and laboratory tests. Patients in the dose expansion phase were evaluated for tolerability and preliminary evidence of anti-tumor activity. Descriptive analyses of anti-tumor activity included evaluation of ORR, DOR, PFS, and duration of stable disease.

Protocol Amendments

The original protocol (Version 1), dated April 4, 2012 was amended 13 times. The most recent version was dated November 24, 2015.

Key protocol revisions include the following:

- Amendment 4 (dated March 27, 2013): Increased sample size to approximately 85 patients; added Schedule 2 and 3
- Amendment 5 (dated June 26, 2013): Increased sample size to approximately 154 patients
- Amendment 6 (dated November 11, 2013): Increased sample size to 249 patients and increased the number of arms from 2 to 6
- Amendment 7 (dated July 2, 2014): Added Arm 7; added Schedules 9 and 10; stopped enrollment in Schedules 1, 2, and 4; increased sample size to 291 patients
- Amendment 8 (dated October 29, 2014): added secondary objective to assess OS; added dose evaluation Arm 8; made dose adjustments for doses above 35 mg/m^2 after determination of MTD and RP2D
- Amendment 10 (dated January 29, 2015): Reduced starting doses for Arms 1, 3, 4, 5, and 6 from 60 mg/m^2 to 35 mg/m^2 or 45 mg/m^2

Data Quality and Integrity: Sponsor's Assurance

The Applicant submitted this NDA, including the clinical study report and data files for study KCP-330-001, to the FDA CDER Electronic Document Room (EDR). The data in this submission are in Electronic Common Technical Document (eCTD) format, in accordance with FDA guidance on electronic submissions. Define files were included for the datasets.

7.2.5 Study Results

Compliance with Good Clinical Practices

The Applicant provided attestation that this study was conducted in accordance with the ethical principles from the Declaration of Helsinki, and in accordance with the Sponsor's procedures, which are consistent with International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), and applicable local regulations.

Financial Disclosure

The Applicant stated that information regarding financial disclosures was obtained from all Investigators. Financial disclosure forms were not collected for 8 investigators at site (b) (6) because they were either erroneously added to the Form FDA 1572 dated March 29, 2016 and subsequently removed, or they were listed on the Form FDA 1572 dated August 21, 2015, but the site later confirmed by email that they did not participate in the trial. Financial disclosure forms were not collected for 2 investigators at site (b) (6). It was confirmed that one investigator was added to the Form FDA 1572 in error and the other investigator left the institution prior to approval of the trial.

Reviewer Comment: None of these issues are anticipated to affect the integrity of the trial.

Patient Disposition

In total, the study enrolled 82 patients with RRMM and 81 patients received at least one dose of selinexor. Patient enrollment by arm and treatment by dose schedule are summarized in Table 29.

Table 29: KCP-330-001 Study Arms and Dose Schedules for Patients with RRMM

Arm (N)	Schedule 1	Schedule 2	Schedule 3	Schedule 4	Schedule 5	Schedule 6	Schedule 11
Arm 1 (N = 45)	4	10	27*	2	2	NA	NA
Arm 6 (N = 25)	NA	NA	NA	NA	NA	25	NA
Arm 8 (N = 11)	NA	NA	NA	NA	NA	NA	11

*Dose expansion cohort
(Source: FDA Analysis)

Efficacy Results - Primary Endpoint

Of all 81 patients with RRMM treated in KCP-330-001, 7 patients responded, corresponding to an ORR of 8.6%, including 1 patient who achieved a sCR and 6 patients who achieved a PR (Table 30). Of the 25 patients who received selinexor plus dexamethasone, the ORR was 24%. Of the patients who received single-agent selinexor (N=56), 1 patient achieved a PR, corresponding to an ORR of 1.8%.

Table 30: KCP-330-001 Preliminary Efficacy Results

Response Category	All RRMM (N = 81) n (%)	Selinexor + Dexamethasone (N = 25) n (%)	Selinexor Monotherapy (N = 56) n (%)
ORR	7 (8.6)	6 (24)	1 (1.8) *
sCR	1 (1.2)	1 (4)	0
CR	0	0	0
VGPR	0	0	0
PR	6 (7.4)	5 (20)	1 (1.8) *

* Patient received dexamethasone as a concomitant medication
(Source: FDA Analysis)

Reviewer Comment: Of the 56 patients with RRMM who received selinexor as monotherapy, only one patient responded, and of note, this patient received dexamethasone 12 mg twice weekly with selinexor as a concomitant medication. Therefore, selinexor demonstrated essentially no single-agent activity. The ORR of 24% observed for patients who received selinexor plus dexamethasone is similar to the ORR observed in Part 2 of STORM.

Data Quality and Integrity - Reviewers' Assessment

The overall quality and integrity of the application was acceptable.

Dose/Dose Response

Refer to the Clinical Pharmacology section of this review for details regarding dose and dose response in study KCP-330-001.

7.2.6 KS-50039 (Retrospective observational study using real-world data)

Overview and Objective

The FDA recently published a Framework for FDA's Real-World Evidence Program (FDA, 2018) for evaluating the potential use of real-world evidence data (RWD) to help support the approval of new indications for a drug already approved under the Federal Food, Drug, and Cosmetic Act (FD&C Act) Section 505(c) or to help support or satisfy drug post-approval study requirements. In addition, the FDA published a guidance document on Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data in 2013 (FDA, 2013). These two documents, as well as published literature (Public Policy Committee, 2016; Wang, 2017), outline the principles and considerations when observational studies are performed to generate evidence for regulatory decision-making. To enhance transparency and facilitate evaluation of validity, FDA requires submission of study protocols and statistical analysis plans (SAP) prior to study initiation. Pre-specification of study protocols and SAPs can preclude unplanned multiple testing and analyses, which may inflate Type I error probability and lead to spurious or un-reproducible findings. In support of NDA 212306 for selinexor, the Applicant submitted analyses using retrospectively collected electronic health record (EHR) data. However, neither the protocol or SAP for the selinexor RWD analysis was submitted to FDA prior to the conduct of the study. FDA was made aware of Study KS-50039 upon receiving the final study report on October 6, 2018.

Study KS-50039 was a retrospective observational study using EHR data, also referred to as real-world data (RWD) in this document, from the Flatiron Health Analytic Database (FHAD) with the goals of characterizing the survival of a population similar to that studied in Part 2 of STORM and comparing the OS results from the RWD to the OS results from Part 2 of STORM.

Without having reviewed and consented to a protocol and SAP, FDA cannot be certain that the protocol and SAP were pre-specified and unchanged during the data selection and analyses. Further, upon receipt of the NDA and the RWD study, FDA requested the Applicant address several issues that presented challenges for comparison of the two study samples. These issues, and how the Applicant addressed them, are discussed in more detail below. The summary of FDA's information requests (IR) and the Applicant's response to FDA IRs are included in Appendix 13.5.

This review discusses the Applicant's initially submitted data and analyses, as well as updated analyses after FDA's IR on December 12, 2018.

FHAD Selection Criteria Issues

In the Applicant's original NDA submission, a total of 64 patients were selected from the Flatiron Health Analytic Database (FHAD). The inclusion and exclusion criteria used to identify patients for Part 2 of STORM and the FHAD analysis are compared side by side in Table 31 (see Appendix 13.5 for full eligibility criteria for STORM Part 2), and the selection steps used to identify the FHAD cohort are shown in Figure 6. Substantial differences in the inclusion and exclusion criteria for the STORM and FHAD cohorts are likely to result in selection bias, misclassification, and confounding. For example, the Applicant cited real-world OS of patients

with penta-exposed, triple-class refractory MM as 3.5–3.7 months; however, patients with less than 4 months life expectancy were excluded from STORM. An exclusion criterion for minimal life expectancy was not implemented for the FHAD population. Differences in selection criteria between the study arms systematically ensure that the STORM cohort will have longer expected OS compared to FHAD cohort.

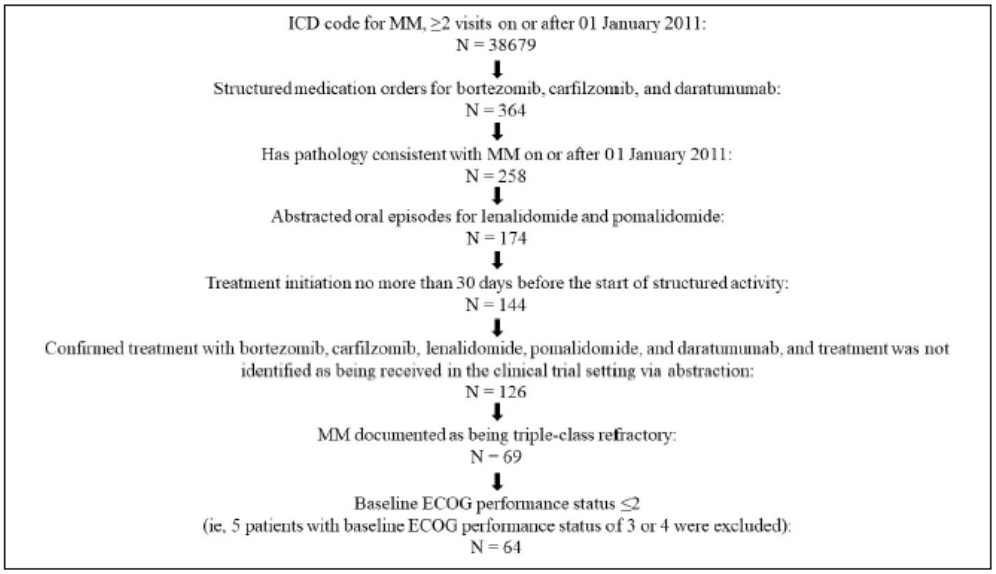
Table 31: Selected Eligibility Criteria for STORM and FHAD

STORM	FHAD
Inclusion Criteria	
Histologically confirmed diagnosis, measurable disease and evidence of disease progression. Symptomatic MM based on IMWG guidelines. Measurable disease as defined by at least one of the following: 1. Serum M-protein ≥ 0.5g/dL by serum electrophoresis (SPEP) or for IgA myeloma, by quantitative IgA; or 2. Urinary M-protein excretion at least 200mg/24 hours; or 3. Serum Free Light Chain (FLC) whereby the involved light chain measures ≥ 10 mg/dL and with an abnormal light chain ratio.	1. International Classification of Diseases (ICD) diagnosis of MM (ICD-9 203.0x or ICD-10, C90.0x, C90). 2. 2+ documented clinical visits on or after 01/01/2011. 3. Pathology consistent with MM.
Patient must have received ≥ 3 anti-MM regimens including the following: an alkylating agent, lenalidomide, pomalidomide, bortezomib, carfilzomib and a glucocorticoid.	Treatment with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab (i.e. Penta-exposed).
N/A	Treatment initiation no more than 30 days before the start of structured activity (excludes patients with potentially missing structured Flatiron data).
Multiple myeloma refractory to the patient's most recent anti-MM regimen.	Documentation of having MM refractory to (1) at least 1 PI (bortezomib or carfilzomib), (2) at least 1 IMiD (lenalidomide or pomalidomide), and (3) daratumumab.
Laboratory data establishing: 1. Adequate hepatic functioning 2. Adequate renal functioning 3. Adequate hematopoietic function	No similar criteria.
Exclusion Criteria	
Life expectancy < 4 months	No similar criteria.
N/A	Lack relevant unstructured documents in the Flatiron database for review by the abstraction team

No similar criteria.	Treatment exposure to lenalidomide, pomalidomide, bortezomib, carfilzomib, or daratumumab was in the clinical trial setting.
Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 2	Patients were excluded if their baseline ECOG Performance Status was 3 or 4.
Smoldering MM, plasma cell leukemia, MM that does not express M-protein or FLC, active CNS MM.	No similar criteria.
Radiation, chemotherapy, immunotherapy or any other anticancer therapy ≤ 2 weeks prior to Cycle 1 Day 1 (C1D1); radio-immunoassay 6 weeks prior to C1D1; major surgery within 4 weeks prior to C1D1.	No similar criteria.
Not adequately recovered from the side effects of previous antineoplastic agents prior to dosing.	No similar criteria.
Active graft versus host disease after allogeneic stem cell transplantation; unstable cardiovascular function; uncontrolled hypertension; uncontrolled active infection; HIV seropositive; hepatitis A, B, or C infection; prior malignancies; GI dysfunction; Grade ≥ 2 neuropathy; other serious psychiatric or medical conditions	No similar criteria.

(Source: FDA)

Figure 6: Attrition Diagram for Selection of Patients in FHAD



ECOG: Eastern Cooperative Oncology Group; ICD: International Classification of Diseases; MM: multiple myeloma.

(Source: Applicant's KS-50039 Study Report Dated August 6, 2018)

Index Date Issues

Systematic differences in how the index date was defined may have resulted in biased results. Overall survival is defined as the time from the index date until death by any cause. The definition of the index date has a direct effect on the length of the observed survival time intervals. Systematic differences in the way the index date is determined across the treatment arms can be a source of bias. Randomizing treatment assignments in clinical trials controls for known and unknown confounders, including those associated with the initial point (index date) of a patient's survival interval. We highlight this point because the index date is directly related to the OS endpoint and systematic differences in the index date across treatment arms will directly impact estimation of differences in OS. We expand on this point further in this appendix.

The results from the primary analysis are displayed in Table 32. Due to major methodological issues (including immortal time bias, selection bias, misclassification, confounding, and missing data), the FDA does not consider these results adequate to support regulatory decision making.

Table 32: Unadjusted OS by Study Population

	FHAD (N = 64)	**STORM (N = 122)**
Death, n (%)	31 (48.4)	49 (40.2)
Median OS, months (95% CI)	3.7 (2.6, 7.1)	9.5 (7.3, 11.9)
HR (95% CI)	0.41 (0.26, 0.65)	
P-value	0.0001	

(Source: Applicant's KS-50039 Study Report Dated August 6, 2018)

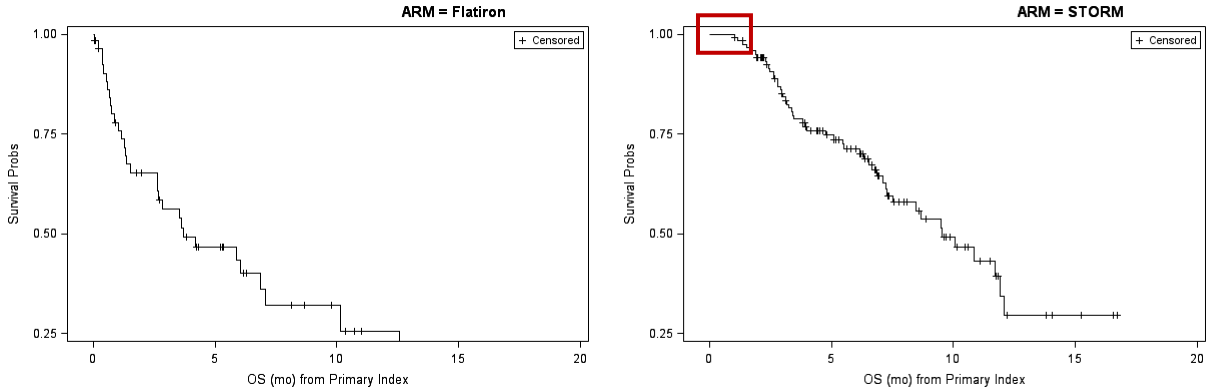
The index dates were originally defined as follows:

- FHAD: the end date of the regimen for which the patient's MM may first be defined as penta-exposed. (Note, this date could be earlier than the date on which the patient's MM could be defined as triple-class refractory)
- STORM: the progression date of the last line of therapy prior to selinexor initiation (Note, all STORM patients were penta-exposed, triple-class refractory)

The index date to start assessment of overall survival, for both the STORM trial and FHAD, was the date upon which a patient failed his or her last treatment. Using this index date, some FHAD patients could have exhausted all treatment options and could not be indexed at their next treatment (note that 27/64 FHAD patients had no subsequent treatment and should have been excluded from the study). However, in STORM, all patients must survive until randomization (initiation of selinexor) by design. Thus, person-time between failure of the prior therapy and randomization is "immortal" by design in STORM. It is unknown how many

months of immortal time this represents on average. From the survival plot below (Figure 7), the first outcome/censoring event in the STORM trial appears to be at approximately 1.2 months. At this time, approximately 22% of the FHAD patients had died or been censored (highlighted in red in Figure 7).

Figure 7: Unadjusted OS by Study Population



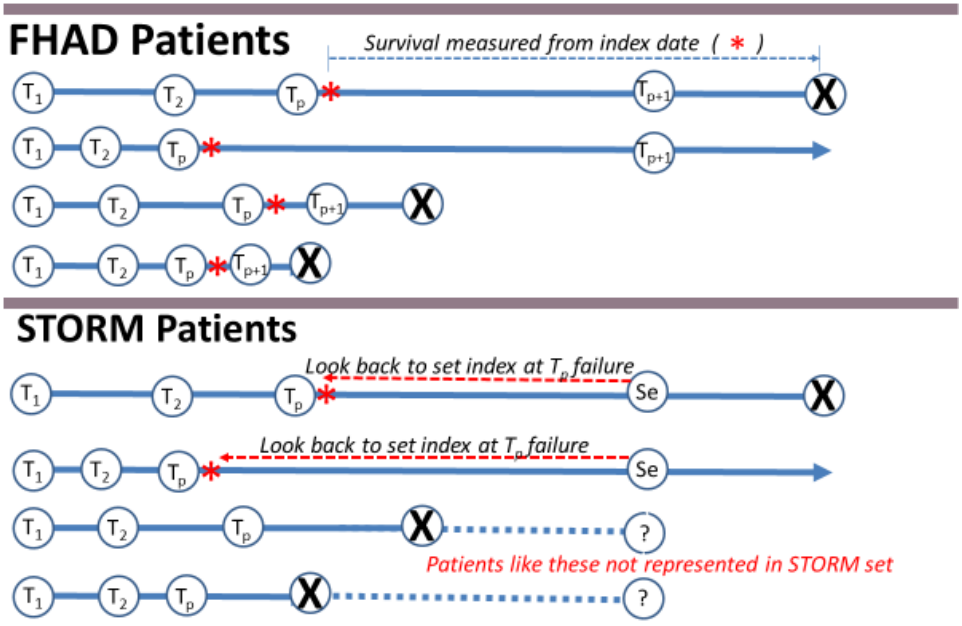
Note: Red box represents minimum level of immortal time bias.
(Source: FDA Analysis)

Additionally, the Applicant's report notes that FHAD patients were indexed on the day they became penta-exposed, but not necessarily on the day they became triple-class refractory. Given the short-observed survival in the FHAD cohort, many FHAD patients may not have survived long enough to reach the same prior therapy definition as in the STORM study, and thus they are likely not an appropriate comparison. This is further evidenced by the fact that STORM patients had mean time from diagnosis to index date of 78.1 months versus 42.1 months for the FHAD patients.

The index date for both the STORM trial and FHAD should be the day of study treatment initiation after becoming penta-exposed and triple-class refractory. This definition of index date was suggested by FDA during a meeting with the Applicant on December 19, 2018 and requested by FDA in an IR sent on January 4, 2019. The index date was updated for the Applicant's sensitivity analyses submitted on January 11, 2019.

The original index date definitions induce immortal time bias in the results of the study (Figure 8). In other words, for patients to be in the selinexor treatment arm, they are required to have lived long enough to enroll on the study. Patients on the FHAD arm do not have this requirement. The immortal time bias in the KS-50039 study manifests itself as the plateau in the STORM Kaplan-Meier curve (Figure 7, above).

Figure 8: Immortal Time/Selection Bias



(Source: FDA)

In Figure 8 (above), each line represents a hypothetical patient; the circles containing letters represent treatment regimens; T_p represents the treatment after which a patient may be considered triple-class refractory; X represents death. The index date is set at treatment T_p failure for all patients. To set the index date for patients in STORM according to the above definition, one must look back into the patients record to determine the failure date of the previous regimen. This requirement excludes patients who do not live long enough to enroll in STORM. In contrast, patients with short survival times are not systematically excluded from the FHAD set.

Comparability Issues

In addition to difference in inclusion and exclusion criteria as shown in Table 31 (above), additional factors result in a lack of comparability between the FHAD and STORM cohorts. The RWD analysis compares patients in STORM, who are sufficiently healthy to enroll in a clinical trial, versus patients in FHAD who may or may not receive additional therapy. Patients who have failed their current treatment but do not receive another treatment likely have a lower expectation for overall survival. Clinical trial patients, who would likely have been more similar to the STORM cohort, were explicitly excluded from the FHAD cohort. Although page 61 of the Applicant's ODAC Briefing Document states, "The demographics of the patients in STORM are representative of real-world patients with triple-class refractory multiple myeloma," imbalances in baseline characteristics between the FHAD and STORM cohorts were noted (Table 33). For example, the FHAD had different prior treatment histories, and differential distributions of ECOG scores and missing data. Imbalances between treatment groups were not adequately accounted for in the design or analysis phases, which likely resulted in confounding

bias, primarily favoring survival for the STORM cohort. For example, though the Applicant excluded FHAD patients with ECOG >2, the 31% of patients with missing ECOG scores were grouped with patients with ECOG = 0. Consequently, the FHAD cohort likely includes more patients with a worse ECOG score, biasing towards shorter survival compared to the STORM cohort.

Although the STORM cohort is more heavily pretreated (median of 7 therapies; 78 months since initial diagnosis) than the FHAD cohort (median of 5 therapies; 42 months since initial diagnosis), it is erroneous to conclude that the STORM cohort has a worse prognosis. The opposite is also a possibility, where the STORM cohort is depleted of patients susceptible to early mortality (termed depletion of susceptibles). Patients who survived with their condition for a longer time may also be capable of surviving longer while on treatment.

Table 33: Incomparable Baseline Characteristics Using the Original Index Date

Parameter	**FHAD (N=64)**	**STORM (N=122)**
Age (years)		
Mean (SD)	66.2 (9.3)	63.8 (9.3)
Sex, n (%)		
Male	33 (51.6)	71 (58.2)
Female	31 (48.4)	51 (41.8)
Race, n (%)		
White	38 (59.4)	78 (69.3)
Non-White	26 (40.6)	44 (36.1)
Prior Therapy		
Carfilzomib, pomalidomide, and daratumumab	34 (53.1)	117 (95.9)
Median number of prior regimens (min, max)	5 (2, 8)	7 (3, 18)
Daratumumab as last line prior to index date, n (%)	43 (67.2)	58 (47.5)
Exposed to anthracyclines prior to index date, n (%)	7 (10.9)	45 (36.9)
Exposed to alkylating agent prior to index date, n (%)	41 (64.1)	122 (100)
Stem cell transplant prior to index date, n (%)	38 (59.4)	102 (83.6)
Immunoglobulin Subtype		
IgA or IgM, n (%)	16 (25)	18 (14.8)
ECOG Performance Status, n (%)		
0	4 (6.3)	37 (30.3)
1	33 (51.6)	71 (58.2)

2	7 (10.9)	11 (9)
Missing	20 (31.3)	3 (2.5)
R-ISS, n (%)		
I	11 (17.2)	20 (16.4)
II/Unknown	50 (78.1)	79 (64.8)
III	3 (4.7)	23 (18.9)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; FHAD = Flatiron Health Analytic Database; Ig = immunoglobulin; max = maximum; min = minimum; R-ISS = Revised International Staging System; SD = standard deviation; STORM = Study KCP-330-012.
(Source: FDA Analysis)

It is likely that differences in patient populations at baseline cannot be fully assessed due to incomplete baseline covariate data. For example, there is no baseline laboratory or comorbidity data, and baseline tumor stage status is mostly unknown (65-78% II/Unknown) in the FHAD cohort. Further, there is likely differential misclassification and measurement error because the data for the selinexor patients vs. FHAD comparison patients originate from different sources. Clinical trial data can be expected to be much more precise and complete compared to RWD. During clinical trials, data collection is standardized and collected at regular, pre-specified intervals. The same is not true of RWD.

To create more comparable patient populations between FHAD and STORM, the Applicant performed propensity score (PS) weighted analyses using inverse probability of treatment weight (IPTW). However, the required assumptions (i.e. adequate sets of prognostic factors; an adequate sample size; strict positivity) for the PS matching or weighted analyses may not be met based on current data (Austin, 2009, 2011; Stuart, 2010). FDA noticed that some important covariates were not incorporated in the analyses (e.g. time from diagnosis to the Index Date; stem cell transplantation prior to Index date) and some covariates are not well balanced even after the weighted analyses, particularly, the numbers of prior regimens, time from diagnosis to index day, and percent with prior stem cell transplantation.

As will be discussed below, once the data selection criteria issues are addressed, modeling and PS methods are no longer feasible due to small sample sizes.

Additional Analyses

On December 12, 2018, the FDA requested the Applicant to address several issues with the study KS-50039 data sets (i.e., FHAD), including immortal time bias and lack of comparability across cohorts.

In attempt to address immortal time bias, the FDA requested that the index date for the STORM patients be defined as the start date of selinexor initiation, or as the start date of the next treatment after becoming penta-exposed and triple-class refractory in the FHAD set.

To explore and address the lack of comparability, the FDA requested that the Applicant consider criteria to achieve greater comparability across comparison cohorts. Specifically, the FDA found that the original criteria used to identify patients in the FHAD population differed from the eligibility criteria for patients in the STORM population in key aspects which limit the ability to compare the two populations and may bias the overall survival results in favor of the STORM population.

- Patients in STORM were required to meet criteria for having previous treatment with an alkylating agent, measurable disease based on IMWG criteria (e.g. serum M-protein ≥0.5g/dL, urinary M-protein excretion ≥200mg/24hrs, FLC ≥100mg/L), and adequate renal, hepatic and hematologic function (e.g., platelet count, hemoglobin, etc.).

- Patients with smoldering MM, plasma cell leukemia, amyloidosis, central nervous system MM, graft vs host disease at C1D1, unstable cardiovascular function, HIV seropositivity, hepatitis A, B, or C infection, prior malignancy that required treatment or has shown evidence of recurrence, Grade ≥3 peripheral neuropathy or Grade ≥2 painful neuropathy, receipt of transfusions, and life expectancy < 4 months were excluded from STORM.

Furthermore, the Applicant excluded patients from the FHAD population who had treatment exposure to lenalidomide, pomalidomide, bortezomib, carfilzomib, or daratumumab in the clinical trial setting.

FDA also noted in the IR, that to be comparable to the STORM population, the FHAD population should be one that is receiving active anti-myeloma therapy. In the original dataset submitted to the FDA, 28 (44%) patients in the FHAD population did not receive subsequent anti-myeloma therapy.

In the 1/4/2019 IR, FDA stated that, to avoid confounding, patients in the STORM dataset who received treatments after meeting the penta-exposed and triple class refractory criteria, but before selinexor should be excluded from a comparison of survival times.

The Applicant responded to the FDA 12/12/2018 and 1/4/2019 IRs on 1/11/2019 with an updated data set that included 37 patients in the FHAD arm and 64 patients from the STORM trial. Although the Applicant updated the index date definition per FDA's recommendation, evidence of incomparability across baseline characteristics persisted. Table 34 displays the major incomparable baseline characteristics using the updated index data. The Applicant's OS analysis results and Kaplan-Meier Survival Curves for both FHAD and STORM by the updated index date are shown in Table 35 and Figure 9.

Table 34: Incomparable Baseline Characteristics Using the Updated Index Date

Baseline Status	FHAD (N = 37)	STORM (N = 64)
Median time from initial diagnosis to index date (months)	40.4	77.3
Initial diagnosis before Jan 1st, 2011, n (%)	0	30 (46.9)
Baseline platelets ≥ 50,000 mm^3, n (%)	31 (83.8)	64 (100)
Baseline hemoglobin > 8 g/dL, n (%)	26 (70.3)	64 (100)
Exposed to alkylating agent prior to index date, n (%)	21 (56.8)	64 (100)
Stem cell transplantation prior to index date, n (%)	22 (59.5)	53 (82.8)

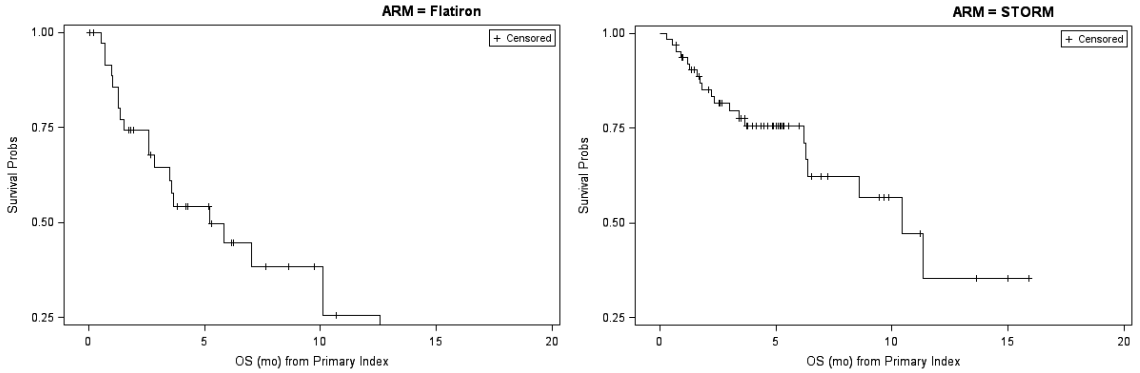
(Source: FDA Analysis)

Table 35: OS in FHAD and STORM Using the Updated Index Date

	FHAD (N = 37)	STORM (N = 64)
Death, n (%)	20 (54.1)	20 (31.3)
Median OS, months (95% CI)	5.2 (2.6, 12.6)	10.4 (6.3, NE)
HR (95% CI)	0.49 (0.26, 0.91)	
P-value	0.0241	

(Source: Applicant's Response to Information Request Dated January 11, 2019)

Figure 9: Kaplan-Meier Curves for OS in FHAD and STORM with Updated Index Date



(Source: Applicant's Response to Information Request Dated January 11, 2019)

As previously mentioned, without having reviewed and consented to a protocol and SAP, FDA cannot be certain that the protocol and SAP were pre-specified and unchanged during the data selection and analyses. This uncertainty and the knowledge that subsequent unmasked analyses have been performed could lead to overly optimistic conclusions.

We note that the Applicant performed sensitivity analyses using the updated data sets containing 37 FHAD and 64 STORM patients by adjusting the inclusion of patients based on

several criteria. The results are summarized in Table 36 below. The analyses adjusted each factor one at a time. To be conservative, several or all of the factors should be adjusted together. Moreover, several of the factors used in the sensitivity analyses are inclusion criteria for STORM. For the STORM and FHAD data sets to be compatible, the FHAD data set should be modified to follow these criteria.

Table 36: Sensitivity Analyses of OS Using the Updated Index Date and Selection Criteria

Sensitivity Analysis	FHAD: N Median OS (95% CI)	STORM: N Median OS (95% CI)	Hazard Ratio (95% CI)	P-value
Exclude Patients with Concomitant Plasma Cell Leukemia	36 5.8 (2.6, 12.6)	64 10.4 (6.3, NE)	0.50 (0.27, 0.94)	0.0315
Only Include Patients with Adequate Hepatic Function	29 5.8 (2.8, 12.6)	62 10.4 (6.3, NE)	0.51 (0.26, 0.99)	0.0455
Only Include Patients with Adequate Renal Function	35 5.2 (2.6, 10.1)	63 10.4 (6.3, NE)	0.43 (0.23, 0.890)	0.0081
Only Include Patients with Platelet Count ≥ 50,000 mm^3	31 5.2 (2.6, 12.6)	64 10.4 (6.3, NE)	0.52 (0.27, 1.01)	0.0528
Only Include Patients with Hemoglobin Level > 8 g/dL	26 10.1 (2.6, 12.6)	64 10.4 (6.3, NE)	0.58 (0.28, 1.18)	0.1316
Only Include Patients with Prior Use of Alkylating Agent	21 5.8 (1.5, 12.6)	64 10.4 (6.3, NE)	0.52 (0.25, 1.09)	0.0827
Only Include Patients with Prior Stem Cell Transplant	22 5.8 (2.6, 12.6)	53 10.4 (6.4, NE)	0.44 (0.21, 0.95)	0.0357
Exclude Patients with 17p Deletion	35 5.8 (2.8, 12.6)	51 10.4 (6.3, NE)	0.53 (0.27, 1.04)	0.0648
Only Include Patients with 7 or Fewer Prior Regimens	37 5.2 (2.6, 12.6)	40 10.4 (3.7, NE)	0.59 (0.31, 1.15)	0.1245

(Source: Applicant's Response to Information Request Dated January 11, 2019)

Key inclusion and exclusion criteria not addressed completely in the FHAD data set construction are:

- Platelets ≥ 75,000/mm^3 for patients with <50% of bone marrow nucleated cells are plasma cells, or ≥ 50,000/mm^3 for patients with ≥50% of bone marrow nucleated cells are plasma cells (patient platelet counts are equal to or greater than 50,000/mm^3)
- Hemoglobin level > 8.5g/dL (>8.0 g/dL with approval from medical monitor)
- Patients must have had prior alkylating agents

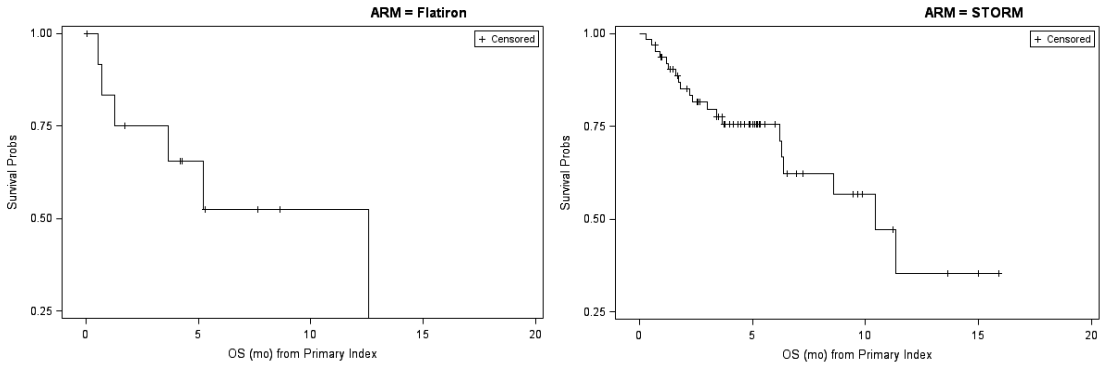
When the data set is modified to meet these three criteria, the number of eligible patients in the FHAD set becomes 13. This data set is likely too small to be representative and the analysis is underpowered to show a difference between the study groups. FDA analysis using the 13 patients from FHAD and 64 patients from STORM is shown in Table 37 and Figure 10. As seen from the results, the hazard ratio is 0.63 with 95% confidence interval of (0.25, 1.58).

Table 37: FDA Analysis of OS Using Updated Index Date and Selection Criteria

	FHAD (N = 13) *	**STORM (N = 64)**
Median OS, months (95% CI)	12.6 (0.7, 12.6)	10.4 (6.3, NE)
HR (95% CI)	0.63 (0.25, 1.58)	
P-value	0.33	

* Patients with platelets ≥ 50,000 mm^3, hemoglobin > 8 g/dL, and prior use of alkylating agent(s)
(Source: FDA Analysis)

Figure 10: Kaplan-Meier Curves for OS Using Updated Index Date and Selection Criteria



(Source: FDA Analysis)

Conclusions

Given the methodological limitations discussed above, we conclude that the evidence generated from the RWD analysis is not adequate to provide context or comparison for the overall survival observed in the STORM patients. This conclusion is based on the lack of comparability between the STORM and FHAD treatment groups. Furthermore, FDA's analysis

finds that post-hoc strategies to create greater comparability across cohorts were inadequate and resulted in very limited sample size and unstable estimates.

7.3 Integrated Review of Effectiveness

7.3.1 Assessment of Efficacy Across Trials

Only one pivotal trial (STORM) was submitted, and therefore, the integrated assessment of efficacy across trials is not applicable.

7.3.2 Integrated Assessment of Effectiveness

The efficacy of selinexor in combination with dexamethasone was primarily based on the results of Part 2 of study KCP-330-012 (STORM), a phase 2, open-label, single-arm trial, with supportive evidence from Part 1 of STORM, the phase 1 trial KCP-330-001, and additional information from the ongoing phase 3 randomized trial, KCP-330-023 (BOSTON), evaluating selinexor in combination with bortezomib and dexamethasone compared to bortezomib and dexamethasone alone. A total of 202 patients were enrolled and treated in STORM, including 79 patients in Part 1, and 123 patients in Part 2. Efficacy was also evaluated in a subpopulation of Part 2 (revised mITT population), consisting of 83 patients who received at least four prior lines of therapy and whose MM was refractory to at least two PIs, at least two IMiDs, and an anti-CD38 mAb ("BCLPD-R" population). The primary endpoint was ORR according to IMWG Criteria, as assessed by an IRC. The efficacy results are as follows:

- The ORR in the mITT population consisting of 122 patients in Part 2 of STORM who had at least three prior lines of therapy and who disease was refractory to at least one PI, one IMiD, and an anti-CD38 mAb was 25.4% (95% CI: 18%, 34.1%).
- The median DOR in the mITT population was 4.4 months (range 0.8 to 9 months).
- Responses in the mITT population included 2 patients with sCR, 6 patients with VGPR, and 23 patients with PR.
- The ORR in the BCLPD-R subgroup was 25.3% (95% CI: 16.4%, 36%).
- The median DOR in the BCLPD-R subgroup was 3.8 months (range 0.7 to 8.1 months).
- Responses in the BCLPD-R subgroup included 1 patient with sCR, 4 patients with VGPR, and 16 patients with PR.
- There was a trend towards decreased response rate in patients enrolled at sites outside of the U.S. (ORR 13.2%, 95% CI: 4.4%, 28.1% for this subgroup in Part 2), and increased response rate in patients with free-light chain only MM (ORR 45%, 95% CI 23.1%, 68.5% for this subgroup in Part 2).

7.4 Review of Safety

The clinical review of safety is primarily based on safety data from KCP-330-012 (STORM), supported by safety findings from study KCP-330-001, and pooled safety data from studies KCP-

330-008, KCP-330-009, KCP-330-010, KCP-330-012, KCP-330-023, KCP-330-017, and KCP-330-023.

7.4.1 Safety Review Approach

Safety analyses were conducted on the complete datasets provided by the Applicant for the STORM trial, which used a data cut-off date of April 24, 2018 at the time of the initial NDA submission. At the request of the FDA, the Applicant submitted updated adverse event and exposure analysis datasets (adae2.xpt and adec.xpt) for Part 2 of STORM on February 5, 2019, after the Applicant identified errors in the classification of some dose modifications due to TEAEs in the original ADAE dataset and updated the dataset (ADAE2) to correct the errors. Safety analyses were performed using the original ADAE dataset unless indicated otherwise.

7.4.2 Review of the Safety Database

Overall Exposure

The proposed starting dose of selinexor 80 mg orally in combination with dexamethasone on days 1 and 3 or each week was the lowest dose level studied for selinexor when administered in combination with dexamethasone in patients with RRMM in the phase 1 study KCP-330-001. In STORM Part 1, 51 of the patients received selinexor 80 mg and dexamethasone 20 mg twice weekly on Weeks 1–3 of each 28-day cycle (6 doses per cycle). The remaining 28 patients enrolled in Part 1, and all 123 patients enrolled in Part 2 received 8 doses per cycle. Therefore, of the 202 patients in the primary safety population, 51 (25.2%) were on the 6 doses per cycle regimen and 151 (74.8%) were on the 8 doses per cycle regimen. Many patients required dose modifications (including reduction, interruption, or discontinuation) early in treatment. The median duration of treatment on selinexor 80 mg plus dexamethasone 20 mg twice weekly for patients in Part 2 of STORM (N = 123) was 3.5 weeks (Figure 1).

Reviewer Comment: The frequency of dose modifications early and treatment and short median duration of treatment on the proposed starting dose suggests it is poorly tolerated. A post-marketing commitment is being issued for evaluation of lower doses of selinexor in the proposed patient population.

Relevant characteristics of the safety population

The primary safety population consists of all treated patients in STORM. In total, 202 patients received treatment with selinexor-dexamethasone in Parts 1 and 2 of STORM. The demographics of patients in the safety population are consistent with the demographics of the intended patient population. Demographics information for patients from STORM analyzed for safety is summarized in Table 18. Because of the differences in baseline characteristics (Table 19), prior therapies (Table 20) and the treatment schedule for many of the patients enrolled in

Part 1 (N = 79), the safety results for Part 1, Part 2 (N = 123), and the total population (N = 202) are presented side-by-side.

Adequacy of the safety database

The size of the safety database is adequate to provide a reasonable estimate of adverse reactions that may occur with treatment of selinexor. However, the assessment of safety is limited by the STORM trial design, and there are no randomized data comparing selinexor to either placebo or a standard of care therapy.

7.4.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The quality of the safety data submitted was adequate for substantive primary review. The Applicant provided full datasets for patients enrolled in Parts 1 and 2 of STORM. The Applicant provided patient narratives for all patients in Parts 1 and 2 of STORM who died on or within 30 days of the last dose of study treatment, and all patients who experienced a treatment-emergent serious adverse event (SAE) or a treatment-emergent AE leading to permanent discontinuation of study treatment.

Categorization of Adverse Events

Adverse events (AEs) were reported down to the verbatim term level. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1.

Routine Clinical Tests

The schedule of safety assessments for STORM was described in Section 7.2.1. The frequency of safety monitoring was considered adequate within the context of the study.

7.4.4 Safety Results

An overview of the safety results from STORM is shown in Table 38, which summarizes the categories of treatment emergent AEs (TEAEs) observed in the trial.

Table 38: Overview of TEAEs in STORM

AE Category	Part 1 (N = 79) n (%)	Part 2 (N = 123) n (%)	Total (N = 202) n (%)

Any TEAE	79 (100)	123 (100)	202 (100)
Any Grade 3 or 4 TEAE	75 (94.9)	115 (93.5)	190 (94.1)
Serious TEAE	44 (55.7)	74 (60.2)	118 (58.4)
Discontinuation due to TEAE	21 (26.6)	33 (26.8)	54 (26.7)
Fatal TEAE	8 (10.1)	10 (8.1)	18 (8.9)

(Source: FDA Analysis)

Deaths

Overall, there were 42 deaths on or within 30 days of study treatment in STORM. A total of 19 deaths occurred in patients enrolled in Part 1 and 23 deaths occurred in patients enrolled in Part 2. The FDA reviewed individual patient narratives from all 42 of the on-study deaths to confirm the cause of death. Deaths were attributed to disease progression in cases where there was at least one of the following: (1) objective evidence of disease progression, (2) decision by the treating physician to change therapy, or (3) transition to hospice/palliative care. Approximately half of the deaths (22) were attributable to progressive disease, and the remainder (20) were either due to a TEAE (18) or were attributed to progressive disease by the Applicant but had insufficient information to support this attribution (2 patients in Part 1). All on-study deaths are summarized in Table 39.

Table 39: Deaths in STORM

Reason for Death	**Part 1 (N = 79) n (%)**	**Part 2 (N = 123) n (%)**	**Total (N = 202) n (%)**
All causes	19 (24.1)	23 (18.7)	42 (20.8)
Disease progression	9 (11.4)	13 (10.6) *	22 (10.9)
TEAE	8 (10.1)	10 (8.1)	18 (8.9)
Insufficient information	2 (2.5) †	0	2 (0.5)

* Reason for death updated from "unknown" to progressive disease after data cut-off.
† Subjects (b) (6)
(Source: FDA Analysis)

The causes of death in Part 1 were dyspnea, influenza, cardiorespiratory arrest (2 cases), subdural hematoma, multiple organ dysfunction syndrome, ascites and plasma cell leukemia, and respiratory failure. The causes of death in Part 2 were pneumonia (2 cases), sepsis (2 cases), subdural hematoma, cardiac disorder, fungal sepsis, multiple organ dysfunction syndrome, respiratory arrest, and septic shock.

Reviewer Comment: Regarding the deaths due to TEAEs, the Applicant classified these cases as either "treatment related" or "non-treatment related;" however, it should be noted that in a single arm trial, it is challenging to assess treatment attribution for adverse events in the absence of a control arm. Given the difficulty in ascertaining the baseline incidence of adverse events in a population of patients with advanced MM on a single arm trial, the FDA considers all deaths due to a TEAE in this setting to be treatment-related, unless clearly related to other extraneous causes.

The narratives for the 23 patients who died on or within 30 days of study treatment in Part 2 of STORM are summarized in Table 40.

Table 40: On-Study Deaths in STORM Part 2

Patient ID	Cause of Death	Summary of Narrative	Data to Support Disease Progression
STORM Part 2 Deaths within 30 Day Due to Progressive Disease (N = 13)			
(b) (6)	Disease progression	The patient was a 68-year-old woman diagnosed with stage I IgA kappa MM on (b) (6). She received 7 prior lines of therapy and underwent ASCT twice. She started treatment with 80 mg selinexor twice weekly with 20 mg dex twice weekly on (b) (6) with the last dose taken on Day 24. On Day 19, she had a thoracentesis for malignant pleural effusion. She was hospitalized on Day 32 due to Grade 3 pleural effusion. She was intubated, then extubated and transitioned to nasal cannula on Day 34 after placement of a pigtail catheter. On Day 36, she experienced tachypnea and hypoxia. A pleurex was placed on Day 40. She was discharged to hospice on Day 42 and died on day 52 due to progressive disease.	Day 1: SPEP 5.37 g/dL Day 29: SPEP 4.51 g/dL Day 33: Recurrent malignant pleural effusion, new extramedullary disease on CT

(b) (6)	Disease progression	The patient was a 55-year-old man diagnosed with stage III IgG kappa MM on (b) (6). He received 8 prior lines of therapy, including ASCT. He started treatment with 80 mg selinexor twice weekly with 20 mg dex twice weekly on (b) (6) with the last dose on Day 66. On Day 70, he experienced an SAE of Grade 2 mental status changes and was admitted to the hospital. CT head showed innumerable bone lesions consistent with plasmacytomas with some showing a decrease in size and others showing interval increase. No definite intracranial cause was identified to explain patient's symptoms. Due to dramatically increased urine protein from 58 (units not provided) on (b) (6) (Day 29) to 96 on (b) (6) (Day 64), and a dramatic decrease in ECOG from 2 to 3/4, the patient was withdrawn from the trial. He died on Day 81 due to progressive disease.	Day 1: UPEP 1199/24h, sFLC 1190.1 mg/L Day 43: sFLC 785.1 mg/L Day 64: UPEP 1672 mg/24h, sFLC 1478.9 mg/L
(b) (6)	Disease progression	The patient was a 72-year-old man diagnosed with stage II IgG kappa MM on (b) (6) He received 8 prior lines of therapy. He started treatment with 80 mg selinexor twice weekly with 20 mg dex twice weekly on (b) (6) with the last dose of selinexor on Day 10. On Day 15, he developed epistaxis and was found to have an SAE of Grade 4 thrombocytopenia. Treatment was withdrawn on Day 20 due to disease progression. He died on Day 22 due to disease progression.	Day 1: sFLC 5200 mg/L Day 15: sFLC 13800 mg/L
(b) (6)	Disease progression	The patient was a 65-year-old woman with stage III MM diagnosed on (b) (6). She received 5 prior lines of therapy, including ASCT. She started treatment with 80mg selinexor twice weekly with 20 mg dex twice weekly on (b) (6) with the last dose on Day 31. On Day 12, she was hospitalized with Grade 3 dehydration. She was discharged on Day 14. She died on Day 40 due to progressive disease.	Day 1: SPEP 1.1 g/dL, sFLC 67 mg/dL Day36: SPEP 2.6 g/dL, sFLC 182 mg/dL
(b) (6)	Disease progression	The patient was a 69-year-old woman diagnosed with Stage II IgG kappa MM on (b) (6). She received 5 prior lines of therapy. She started treatment with 80 mg selinexor and 20mg dex twice weekly on (b) (6) with the last dose on Day 3. On Day 6, she was admitted with Grade 3 fatigue and confusional state. On Day 8, she was discharged to hospice. She died on Day 16 due to disease progression.	Day -1: Numerous scattered pleural-based and subcutaneous chest wall nodules Day 8: Worsening pleural effusions

(b) (6)	Disease progression	The patient was a 54-year-old man diagnosed with IgG lambda MM on (b) (6). He received 4 prior lines of therapy, including ASCT. He started treatment with 80 mg selinexor and 20 mg dex twice weekly on (b) (6) with the last dose on Day 24. On Day 8, he was hospitalized due to a Grade 3 hip fracture. On Day 12, the event was considered resolved and he was discharged to a nursing facility for physical therapy and rehabilitation. He died on Day 36 due to progressive disease.	Day 1: SPEP 1.8 g/dL, sFLC 2167 mg/L Day 8: New pathologic fracture Day 27: SPEP 2.4 g/dL, sFLC 4925 mg/L
(b) (6)	Disease progression	The patient was a 64-year-old man diagnosed with stage III MM on (b) (6) He received 6 prior lines of therapy, including ASCT. He started treatment with 80 mg selinexor and 20 mg dex twice weekly on (b) (6) with the last dose on Day 75. On Day 24 he was diagnosed with Grade 3 non-neutropenic colitis. He was admitted to the hospital with delirium and CT abdomen/pelvis with oral contract showed colitis/proctitis. C. difficile toxin was negative. He was discharged home on Day 30 and had no recurrent SAE of diarrhea or colitis after resuming selinexor on Day 38. He died on Day 89 due to progressive disease.	Day 1: UPEP 332 mg/24h, sFLC 160 mg/dL Day 15: sFLC 67 mg/dL Day 80: UPEP 601 mg/24h, sFLC 368 mg/dL
(b) (6)	Disease progression	The patient was a 63-year-old man diagnosed with stage III MM in (b) (6) He received 7 prior lines of therapy, including ASCT and allogenic SCT. He started treatment with 80 mg selinexor and 20 mg dex twice weekly on (b) (6) with the last dose on Day 10. He had baseline polyserositis, cachexia, and anorexia after allogeneic SCT. On Day 1, he experienced Grade 2 dyspnea. On Day 4, he was hospitalized with Grade 3 dyspnea due to progression of polyserositis. He had advanced extramedullary disease and died from progressive disease on Day 17.	Day 1: sFLC 1560 mg/L Day 11: sFLC 409 mg/L, advanced progressive extramedullary disease
(b) (6)	Disease progression	The patient was a 62-year-old woman diagnosed with stage III IgG lambda MM in (b) (6) She received 12 prior lines of therapy, including ASCT x3. She started treatment with 80 mg of selinexor and 20 mg dex twice weekly on (b) (6) with the last dose on Day 50. On Day 58, she discontinued treatment due to disease progression (lambda FLC 34.82 mg/dL->93.23 mg/dL, M-spike 4.26 g/dL->5.67 g/dL). She died on Day 77 due to disease progression.	Day 1: SPEP 4.3 g/dL, sFLC 348 mg/L Day 58: SPEP 5.8 g/dL, sFLC 643 mg/dL

(b) (6)	Disease progression	The patient was a 70-year-old man diagnosed with stage I IgG lambda MM in (b) (6) He received 12 prior lines of therapy, including ASCT. He started treatment with 80 mg selinexor and 20 mg dex twice weekly on (b) (6) (b) (6) with the last dose on Day 24. On Day 29 he had disease progression and was admitted with an SAE of Grade 3 acute kidney injury. On Day 32, this worsened to Grade 4, and hemodialysis was initiated. He underwent the last dialysis on Day 51, was discharged home on Day 52, and died at home on Day 53 due to disease progression.	Day -14: SPEP 4.8 g/dL Day 1: sFLC 588 mg/L Day 42: SPEP 7.1 g/dL sFLC 1743 mg/L
(b) (6)	Disease progression	The patient was a 73-year-old woman diagnosed with stage I IgA kappa MM in (b) (6) She received 5 prior lines of therapy. She started treatment with 80 mg selinexor and 20 mg dex twice weekly on (b) (6) with the last dose on Day 24. On day 2, she had an SAE of acute pulmonary edema Grade 4. On Day 6, she was transferred to the ICU. On Day 15, treatment was restarted at a reduced dose of selinexor 60 mg on Day 1 and 40 mg on Day 3. On Day 21, the event of acute pulmonary edema was considered resolved. On Day 26, study treatment was withdrawn due to disease progression, and she died due to disease progression om Day 28.	Day 1: sFLC 84.5 mg/dL Day 26: sFLC 180 mg/dL
(b) (6)	Disease progression	The patient was a 53-year-old man diagnosed with stage III IgG lambda MM on (b) (6) He received 4 prior lines of therapy, including ASCT. He started treatment with 80 mg selinexor and 20 mg dex twice weekly on (b) (6) with the last dose on Day 24. On Day 14, he was hospitalized with Grade 2 ear infection and sinusitis. These were resolved on Day 22. On Day 25 he had progressive disease documented with a large plasmacytoma increased in size and two new plasmacytomas. He was removed from study treatment and died on Day 49 due to progressive disease.	Day 25: Plasmacytoma increased from 14x15cm to 18x15cm and two additional plasmacytomas on PET
(b) (6)	Disease progression	The patient was a 58-year-old woman with stage III IgG lambda MM diagnosed on (b) (6) She received 4 prior lines of therapy, including ASCT. She started treatment with 80 mg selinexor and 20 mg dex twice weekly on (b) (6) with the last dose on Day 57. She was admitted with mental status changes and hallucination Grade 3 on Day 58. On Day 59, labs showed free lambda 16,580 mg/L from baseline 4055 mg/L and study treatment was withheld. She was discharged on Day 64 and died on Day 71 (the reason for death due to progressive disease was updated after the data cut-off).	Day 1: UPEP 4056 mg/24h sFLC 4055 mg/L Day 59: UPEP 10884 mg/24h sFLC 16580 mg/L Bilateral pathologic fractures, new plasmacytoma
STORM Part 2 Deaths within 30 Day Due to TEAEs (N = 10)			

(b) (6)	Fungal Sepsis	The patient was a 62-year-old woman diagnosed with IgG kappa MM in (b) (6) She received 7 prior lines of therapy, including ASCT. She started treatment with 80 mg selinexor and 20 mg dex twice weekly on (b) (6) with the last dose on Day 38. She was diagnosed with Grade 3 fungal infection on Day 35 and admitted to the hospital with dysphagia on Day 43. She developed fever on Day 44, and blood cultures were positive for Candida albicans. She started fluconazole and micafungin, and continued vancomycin and cefepime. MRI on Day 47 showed diffuse osseous metastatic disease. She transitioned to comfort care on Day 54 and died from fungal sepsis on Day 55.	NA
(b) (6)	Subdural Hematoma	The patient was a 59-year-old man diagnosed with IgG kappa MM in (b) (6) He received 11 prior lines of therapy, including ASCT. He started treatment with 80 mg selinexor and 20 mg dex twice weekly on (b) (6) with the last dose on Day 51. On Day 28, he was hospitalized with Grade 4 sepsis and respiratory virus panel positive for influenza A. He was discharged on Day 31. Study treatment was discontinued on Day 51 due to progressive disease. On Day 77, he was hospitalized and found to have a subdural hematoma with subfalcine herniation. He was admitted to hospice and died on Day 78.	NA
(b) (6)	Pneumonia	The patient was a 52-year-old man with stage II IgG kappa MM diagnosed on (b) (6) He received 5 prior lines of therapy, including ASCT. He started treatment with 80 mg selinexor and 20 mg dex twice weekly on (b) (6) with the last dose on Day 11. On Day 14, he presented to the emergency department with fever, chills, and productive cough, and was diagnosed with pneumonia, with respiratory virus panel positive for RSV. He developed worsening hypoxia and transitioned to comfort measures on Day 32 and died on Day 38.	NA
(b) (6)	Sepsis	The patient was a 68-year-old woman diagnosed with stage III MM in (b) (6) She received 4 prior lines of therapy, including ASCT. She started treatment with 80 mg selinexor and 20 mg dex twice weekly on (b) (6) with the last dose on Day 40. On Day 40, she reported left lower quadrant abdominal pain and on Day 42, was admitted to the hospital and diagnosed with Grade 3 Clostridium difficile colitis. She was discharged on Day 53. On Day 56, she presented to the ER with extreme weakness, was found to be febrile and was diagnosed with neutropenic sepsis. She was transferred to another hospital on Day 57 and was taken off study. She died on Day 64 due to sepsis Grade 5.	NA

(b) (6)	Respiratory Arrest	The patient was an 84-year-old man with IgG kappa MM diagnosed on (b) (6) and history of cardiomyopathy/congestive heart failure, atrial fibrillation and chronic kidney disease. He received 6 prior lines of therapy. He started treatment with 80 mg selinexor and 20 mg dex twice weekly on (b) (6) with the last dose of selinexor on Day 36. He was hospitalized on Day 41 with Grade 3 cardiac failure with dyspnea. Study treatment was interrupted on Day 42 due to Grade 4 thrombocytopenia. On Day 61, he died from Grade 5 respiratory arrest.	NA
(b) (6)	Cardiac Disorder	The patient was a 75-year-old man diagnosed with stage II IgG kappa MM on (b) (6) He received 7 prior lines of therapy, including ASCT. He started treatment with 80 mg selinexor and 20 mg dex twice weekly on (b) (6) with the last dose on Day 52. On Day 49, he presented with fever, hypoxia, and diarrhea and was admitted with Grade 3 general physical health deterioration. On Day 63, bronchoalveolar lavage was performed, and cultures were positive for Pneumocystis jirovecii. On Day 68, while hospitalized, he died from Grade 5 cardiac disorder.	NA
(b) (6)	Septic Shock	The patient was a 65-year-old man diagnosed with stage III IgG kappa MM on (b) (6) He received 3 prior lines of therapy, including ASCT. He started treatment with 80 mg selinexor and 20 mg dex twice weekly on (b) (6) with the last dose on Day 8. On Day 9, he was hospitalized with Grade 5 septic shock and died a few hours later.	NA
(b) (6)	Multiple Organ Dysfunction Syndrome	The patient was a 55-year-old man diagnosed with stage III IgG lambda MM on (b) (6) He received 3 prior lines of therapy, including ASCT. He started treatment with 80 mg selinexor and 20 mg dex twice weekly on (b) (6) with the last dose on Day 24. He received an overdose due to taking selinexor 80 mg on Days 5 and 7 in addition to Days 1 and 3 due to misunderstanding and thinking it was to be taken every 2 days. On Day 8, he was hospitalized with Grade 3 tumor lysis syndrome (TLS) and an SAE of Grade 2 overdose. The Grade 3 TLS resolved on Day 13 and he was discharged home. He had worsening thrombocytopenia starting on Day 8 and treatment was withdrawn on Day 22 due to thrombocytopenia. On Day 27, he was hospitalized with Grade 2 epistaxis. On Day 37, he was hospitalized with Grade 4 lung disorder, and tested positive for metapneumovirus and RNA coronavirus. On Day 38, he went into septic shock, acute respiratory distress syndrome, and coagulopathy, and was intubated. He died on Day 39 due to multiple organ dysfunction syndrome complicated by disease progression.	NA

(b) (6)	Pneumonia	The patient was a 78-year-old man with IgG lambda MM diagnosed on (b) (6) He received 9 prior lines of therapy. He started treatment with 80 mg selinexor and 20 mg dex twice weekly on (b) (6) with the last dose on Day 17. On Day 20, he was admitted with Grade 3 asthenia, decreased appetite, and renal failure. On Day 21, he developed a fever and was treated for a possible urinary tract infection. On Day 24, he became febrile again and repeat urine culture was positive for Enterococcus faecalis. A CT scan of the chest was consistent with progression of myeloma and showed new patchy ground glass attenuation concerning for pneumonia. By Day 26, he was minimally responsive with deteriorating clinical condition. He transitioned to comfort measures and died that day.	NA
(b) (6)	Sepsis	The patient was a 67-year-old man diagnosed with MM in (b) (6) He received 12 prior lines of therapy, including ASCT twice. He started treatment with 80 mg selinexor twice weekly with 20 mg dex twice weekly on (b) (6) with the last dose on Day 38. On Day 22, he was hospitalized with Grade 3 circulatory collapse. This resolved on Day 25 and he was discharged home. On Day 38, he had progressive disease and transitioned to palliative care. He died in the hospital from Grade 5 sepsis on Day 55.	NA

Abbreviations: ASCT = autologous stem cell transplantation; dex = dexamethasone; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; sFLC = serum free light chains; NA = not applicable.
*Part of BCLPD-R subpopulation
(Source: FDA Analysis)

Serious Adverse Events

Serious AEs (SAEs) occurred in 60.2% of patients in Part 2 and 55.7% of patients in Part 1 (58.4% overall). SAEs that occurred in >2% of patients overall or in either part of STORM are summarized in Table 41. The most frequent SAEs in Part 2 (occurring in at least 5% of patients) were pneumonia (11.4%), sepsis (8.9%), and mental status changes (6.5%).

Table 41: SAEs in STORM

System Organ Class Preferred Term	**Part 1 (N = 79) n (%)**	**Part 2 (N = 123) n (%)**	**Total (N = 202) n (%)**
Blood and lymphatic system disorders			
Anemia	2 (2.5)	4 (3.3)	6 (3)
Febrile neutropenia	3 (3.8)	0	3 (1.5)
Thrombocytopenia	5 (6.3)	3 (2.4)	8 (4)

Cardiac disorders			
Cardiorespiratory arrest	2 (2.5)	0	2 (1)
Gastrointestinal disorders			
Diarrhea	2 (2.5)	3 (2.4)	5 (2.5)
Nausea	3 (3.8)	2 (1.6)	5 (2.5)
Vomiting	2 (2.5)	1 (0.8)	3 (1.5)
General disorders and administration site conditions	3 (3.8)	6 (4.9)	9 (4.5)
Fatigue [a]	0	4 (3.3)	4 (2)
General physical health deterioration	3 (3.8)	3 (2.4)	6 (3)
Pyrexia			
Infections and infestations			
Influenza [b]	5 (6.3)	1 (0.8)	6 (3)
Pneumonia [c]	3 (3.8)	14 (11.4)	17 (8.4)
Sepsis [d]	1 (1.3)	11 (8.9)	12 (5.9)
Respiratory tract infection [e]	2 (2.5)	1 (0.8)	3 (1.5)
Injury, poisoning and procedural complications			
Fracture [f]	4 (5.1)	4 (3.3)	8 (4)
Fall	2 (2.5)	2 (1.6)	4 (2)
Metabolism and nutrition disorders			
Dehydration	3 (3.8)	3 (2.4)	6 (3)
Hypercalcemia	4 (5.1)	0	4 (2)
Hyponatremia	2 (2.5)	3 (2.4)	5 (2.5)
Psychiatric disorders			
Mental status changes [g]	5 (6.3)	8 (6.5)	13 (6.4)
Renal and urinary disorders			
Acute kidney injury	4 (5.1)	3 (2.4)	7 (3.5)
Respiratory, thoracic and mediastinal disorders			
Dyspnea	2 (2.5)	1 (0.8)	3 (1.5)
Respiratory failure [h]	2 (2.5)	2 (1.6)	4 (2)

[a] Includes terms fatigue and asthenia
[b] Includes terms influenza and H1N1 influenza
[c] Includes terms pneumonia, pneumonia viral, pneumonia influenzal, and pneumocystis jirovecii pneumonia
[d] Includes terms sepsis, septic shock, fungal sepsis, and staphylococcal sepsis
[e] Includes terms respiratory tract infection, upper respiratory infection, and lung infection
[f] Includes terms compression fracture, cervical vertebral fracture, lower limb fracture, and pathological fracture
[g] Includes terms mental status changes, confusional state, and delirium
[h] Includes terms respiratory failure, acute respiratory failure, and respiratory arrest
(Source: FDA Analysis)

Dropouts and/or Discontinuations Due to Adverse Effects

The rates of TEAEs leading to dose modifications, including dose reduction, dose interruption, or permanent discontinuation for patients in STORM are shown in Table 42.

Table 42: Dose Modifications Due to TEAEs in STORM

Action Taken with Selinexor	Part 1 (N = 79) n (%)	Part 2 (N = 123) n (%)	Total (N = 202) n (%)
Dose modification due to TEAE	68 (86.1)	112 (91.1)	180 (89.1)
Dose reduced	27 (34.2)	60 (48.8)	87 (43.1)
Dose interrupted	50 (63.3)	90 (73.2)	140 (69.3)
Treatment permanently discontinued	21 (26.6)	33 (26.8)	54 (26.7)

(Source: FDA Analysis (ADAE2 Dataset))

TEAEs leading to dose reduction (occurring in ≥1% of patients overall) are shown in Table 43.

Table 43: TEAEs Leading to Dose Reduction in STORM

System Organ Class Preferred Term	Part 1 (N = 79) n (%)	Part 2 (N = 123) n (%)	Total (N = 202) n (%)
Blood and lymphatic system disorders			
Neutropenia	2 (2.5)	5 (4.1)	7 (3.5)
Platelet count decreased	0	3 (2.4)	3 (1.5)
Thrombocytopenia	18 (22.8)	39 (31.7)	57 (28.2)
Gastrointestinal disorders			
Nausea	6 (7.6)	5 (4.1)	11 (5.4)
Vomiting	3 (3.8)	0	3 (1.5)
General disorders and administration site conditions			
Fatigue[†]	4 (5.1)	9 (7.3)	13 (6.4)
General physical health deterioration	0	2 (1.6)	2 (1)
Investigations			
Weight decreased	4 (5.1)	3 (2.4)	7 (3.5)
Metabolism and nutrition disorders			
Decreased appetite	3 (3.8)	1 (0.8)	4 (2)

Dehydration Hyponatremia	2 (2.5) 2 (2.5)	0 1 (0.8)	2 (1) 3 (1.5)

†Includes terms fatigue and asthenia
(Source: FDA Analysis)

TEAEs leading to dose interruption (occurring in ≥2.5% of patients overall) are shown in Table 44.

Table 44: TEAEs Leading to Dose Interruption in STORM

System Organ Class Preferred Term	**Part 1 (N = 79) n (%)**	**Part 2 (N = 123) n (%)**	**Total (N = 202) n (%)**
Blood and lymphatic system disorders			
Anemia	4 (5.1)	7 (5.7)	11 (5.4)
Neutropenia	0	11 (8.9)	11 (5.4)
Thrombocytopenia	20 (25.3)	34 (27.6)	54 (26.7)
Gastrointestinal disorders			
Nausea	6 (7.6)	6 (4.9)	12 (5.9)
Vomiting	8 (10.1)	4 (3.3)	12 (5.9)
General disorders and administration site conditions			
Fatigue [a]	6 (7.6)	19 (15.4)	25 (12.4)
Pyrexia	3 (3.8)	3 (2.4)	6 (3)
Infections and infestations			
Pneumonia [b]	2 (2.5)	7 (5.7)	9 (4.5)
Respiratory tract infection [c]	2 (2.5)	6 (4.9)	8 (6.5)
Injury, poisoning and procedural complications Fracture[d]	1 (1.3)	4 (3.3)	5 (2.5)
Investigations			
Weight decreased	2 (2.5)	5 (4.1)	7 (3.5)
Metabolism and nutrition disorders			
Decreased appetite	4 (5.1)	5 (4.1)	9 (4.5)
Hyponatremia	9 (11.4)	5 (4.1)	14 (6.9)
Psychiatric disorders			
Mental status changes [e]	3 (3.8)	3 (2.4)	6 (3)

Renal and urinary disorders Acute kidney injury	2 (2.5)	4 (3.3)	6 (3)

[a] Includes terms fatigue and asthenia
[b] Includes terms pneumonia, atypical pneumonia, and pneumocystis jirovecii pneumonia
[c] Includes terms respiratory tract infection, lung infection and upper respiratory tract infection
[d] Includes terms clavicle fracture, femur fracture, humerus fracture, lower limb fracture, and pathological fracture
[e] Includes terms mental status changes and confusional state
(Source: FDA Analysis)

The most common TEAEs leading to discontinuation of study treatment (occurring in ≥1% of patients) are summarized by preferred term in Table 45 and by system organ class (for patients in Part 2) in Table 46.

Table 45: TEAEs Leading to Permanent Discontinuation in STORM

System Organ Class Preferred Term	**Part 1 (N = 79) n (%)**	**Part 2 (N = 123) n (%)**	**Total (N = 202) n (%)**
Blood and lymphatic system disorders			
Anemia	1 (1.3)	3 (2.4)	4 (2)
Thrombocytopenia	4 (5.1)	4 (3.3)	8 (4)
Gastrointestinal disorders			
Diarrhea	2 (2.5)	2 (1.6)	4 (2)
Nausea	3 (3.8)	7 (5.7)	10 (5)
Vomiting	1 (1.3)	3 (2.4)	4 (2)
General disorders and administration site conditions			
Fatigue [a]	5 (6.3)	9 (7.3)	14 (6.9)
General physical health deterioration	0	2 (1.6)	2 (1)
Infections and infestations			
Influenza	1 (1.3)	1 (0.8)	2 (1)
Pneumonia	0	4 (3.3)	4 (2)
Sepsis [b]	0	2 (1.6)	2 (1)
Investigations			
Weight decreased	1 (1.3)	5 (4.1)	6 (3)
Metabolism and nutrition disorders			
Decreased appetite	3 (3.8)	2 (1.6)	5 (2.5)
Psychiatric disorders			
Mental status changes [c]	3 (3.8)	2 (1.6)	5 (2.5)

a Includes terms fatigue and asthenia

b Includes terms sepsis and septic shock
c Includes terms mental status changes, confusional state, and delirium
(Source: FDA Analysis)

Table 46: TEAEs Leading to Permanent Discontinuation in STORM Part 2 by System Organ Class

System Organ Class	Part 2 (N = 123) n (%)
Blood and lymphatic system disorders	5 (4.1)
Cardiac disorders	1 (0.8)
Ear and labyrinth disorders	1 (0.8)
Gastrointestinal disorders	9 (7.3)
General disorders and administration site conditions	11 (8.9)
Infections and infestations	10 (8.1)
Investigations	5 (4.1)
Metabolism and nutrition disorders	2 (1.6)
Nervous system disorders	2 (1.6)
Psychiatric disorders	2 (1.6)
Renal and urinary disorders	1 (0.8)
Respiratory, thoracic and mediastinal disorders	1 (0.8)

(Source: FDA Analysis)

Significant Adverse Events

NCI-CTCAE Grade 3 and 4 TEAEs are events that are severe, debilitating, or life-threatening. Approximately 94% of patients in STORM experienced at least one Grade 3 or 4 TEAE. The most common Grade 3 or 4 TEAEs that occurred in at least 5% of patients in STORM are summarized in Table 47. The most common Grade 3 or 4 TEAEs (occurring in at least 10% of patients) in Part 2 were anemia (43.2%), leukopenia (12.2%), lymphopenia (11.4%), neutropenia (22%), thrombocytopenia (56.9%), fatigue (23.6%), and hyponatremia (20.3%).

Table 47: Grade 3 or 4 TEAEs in STORM

System Organ Class Preferred Term	**Part 1** **Grades 3-4** **(N = 79)** **n (%)**	**Part 2** **Grades 3-4** **(N = 123)** **n (%)**	**Total** **Grades 3-4** **(N = 202)** **n (%)**
Blood and lymphatic system disorders			
Anemia	29 (36.7)	52 (42.3)	81 (40.1)
Leukopenia	8 (10.1)	15 (12.2)	23 (11.4)
Lymphopenia	6 (7.6)	14 (11.4)	20 (9.9)
Neutropenia	16 (20.3)	27 (22)	43 (21.3)
Thrombocytopenia	51 (64.6)	70 (56.9)	121 (59.9)
Gastrointestinal disorders			
Diarrhea	4 (5.1)	9 (7.3)	13 (6.4)
Nausea	6 (7.6)	12 (9.8)	18 (8.9)
General disorders and administration site conditions			
Fatigue [a]	15 (19)	29 (23.6)	44 (21.8)
General physical health deterioration	0	7 (5.7)	7 (3.5)
Infections and infestations			
Influenza [b]	4 (5.1)	1 (0.8)	5 (2.5)
Pneumonia [c]	4 (5.1)	11 (8.9)	15 (7.4)
Sepsis [d]	1 (1.3)	8 (6.5)	9 (4.5)
Injury, poisoning and procedural complications			
Fracture [e]	3 (3.8)	5 (4.1)	8 (4.0)
Metabolism and nutrition disorders			
Decreased appetite	4 (5.1)	5 (4.1)	9 (4.5)
Hypercalcemia	4 (5.1)	0	4 (2)
Hypercreatinemia	4 (5.1)	0	4 (2)
Hyperglycemia	9 (11.4)	6 (4.9)	15 (7.4)
Hypokalemia	0	7 (5.7)	7 (3.5)
Hyponatremia	19 (24.1)	25 (20.3)	44 (21.8)
Psychiatric disorders			
Mental status changes [f]	7 (8.9)	7 (5.7)	14 (6.9)
Renal and urinary disorders			
Acute kidney injury	4 (5.1)	2 (1.6)	6 (3)

a Includes terms fatigue and asthenia

b Includes terms influenza and H1N1 influenza
c Includes terms pneumonia, atypical pneumonia, pneumocystis jirovecii pneumonia, pneumonia influenzal, and pneumonia viral
d Includes terms sepsis and staphylococcal sepsis
e Includes terms femur fracture, hip fracture, humerus fracture, pathological fracture, cervical vertebral fracture, compression fracture, lower limb fracture
f Includes terms mental status changes, confusional state, and delirium
(Source: FDA Analysis)

Treatment Emergent Adverse Events and Adverse Reactions

All patients in STORM experienced at least one TEAE. The most common TEAEs of any grade that occurred in at least 5% of patients in STORM are shown in Table 48. The most common TEAEs (occurring in at least 20% of patients) in Part 2 were anemia (65.9%), leukopenia (30.9%), neutropenia (38.2%), thrombocytopenia (71.5%), constipation (22%), diarrhea (42.3%), nausea (69.9%), vomiting (37.4%), fatigue (72.4%), weight decreased (48.8%), decreased appetite (53.7%), hyponatremia (35%), and dyspnea (21.1%).

Table 48: TEAEs in STORM

System Organ Class Preferred Term	**Part 1** **All Grades** **(N = 79)** **n (%)**	**Part 2** **All Grades** **(N = 123)** **n (%)**	**Total** **All Grades** **(N = 202)** **n (%)**
Blood and lymphatic system disorders			
Anemia	38 (48.1)	81 (65.9)	119 (58.9)
Leukopenia	19 (24.1)	38 (30.9)	57 (28.2)
Lymphopenia	10 (12.7)	20 (16.3)	30 (14.9)
Neutropenia	21 (26.6)	47 (38.2)	68 (33.7)
Thrombocytopenia	59 (74.7)	88 (71.5)	147 (72.8)
Cardiac disorders			
Tachycardia [a]	10 (12.7)	5 (4.1)	15 (7.4)
Eye disorders			
Vision blurred	9 (11.4)	12 (9.8)	21 (10.4)
Gastrointestinal disorders			
Abdominal pain [b]	7 (8.9)	11 (8.9)	18 (8.9)
Constipation	23 (29.1)	27 (22)	50 (24.8)
Diarrhea	37 (46.8)	52 (42.3)	89 (44.1)
Nausea	60 (75.9)	86 (69.9)	146 (72.3)
Vomiting	36 (45.6)	46 (37.4)	82 (40.6)

General disorders and administration site conditions			
Fatigue [c]	58 (73.4)	89 (72.4)	147 (72.8)
General physical health deterioration	0	9 (7.3)	9 (4.5)
Malaise	2 (2.5)	8 (6.5)	10 (5)
Edema peripheral	4 (5.1)	12 (9.8)	16 (7.9)
Pyrexia	13 (16.5)	19 (15.4)	32 (15.8)
Infections and infestations			
Influenza [d]	7 (8.9)	2 (1.6)	9 (4.5)
Pneumonia [e]	5 (6.3)	17 (13.8)	22 (10.9)
Sepsis [f]	1 (1.3)	12 (9.8)	13 (6.4)
Respiratory tract infection [g]	13 (16.5)	21 (17.1)	34 (16.8)
Urinary tract infection	6 (7.6)	3 (2.4)	9 (4.5)
Injury, poisoning and procedural complications			
Fall	5 (6.3)	13 (10.6)	18 (8.9)
Fracture [h]	5 (6.3)	9 (7.3)	14 (6.9)
Investigations			
Alanine aminotransferase increased	6 (7.6)	11 (8.9)	17 (8.4)
Aspartate aminotransferase increased	3 (3.8)	10 (8.1)	13 (6.4)
Weight decreased	35 (44.3)	60 (48.8)	95 (47)
Metabolism and nutrition disorders			
Decreased appetite	42 (53.2)	66 (53.7)	108 (53.5)
Dehydration	17 (21.5)	11 (8.9)	28 (13.9)
Hypercalcemia	8 (10.1)	4 (3.3)	12 (5.9)
Hypercreatinemia [i]	15 (19.0)	13 (10.6)	28 (13.9)
Hyperglycemia	18 (22.8)	13 (10.6)	31 (15.3)
Hyperkalemia	1 (1.3)	11 (8.9)	12 (5.9)
Hyperuricemia [j]	4 (5.1)	2 (1.6)	6 (3)
Hypocalcemia	8 (10.1)	11 (8.9)	19 (9.4)
Hypokalemia	4 (5.1)	21 (17.1)	25 (12.4)
Hypomagnesemia	10 (12.7)	9 (7.3)	19 (9.4)
Hyponatremia	35 (44.3)	43 (35)	78 (38.6)
Hypophosphatemia	6 (7.6)	8 (6.5)	14 (6.9)
Musculoskeletal and connective tissue disorders			
Arthralgia	6 (7.6)	4 (3.3)	10 (5)
Back pain	9 (11.4)	9 (7.3)	18 (8.9)
Bone pain	8 (10.1)	10 (8.1)	18 (8.9)

Muscle spasms	4 (5.1)	8 (6.5)	12 (5.9)
Muscular weakness	5 (6.3)	4 (3.3)	9 (4.5)
Pain in extremity	4 (5.1)	3 (2.4)	7 (3.5)
Nervous system disorders			
Dizziness	11 (13.9)	19 (15.4)	30 (14.9)
Dysgeusia	10 (12.7)	12 (9.8)	22 (10.9)
Headache	11 (13.9)	9 (7.3)	20 (9.9)
Peripheral neuropathy [k]	7 (8.9)	11 (8.9)	18 (8.9)
Psychiatric disorders			
Anxiety	4 (5.1)	7 (5.7)	11 (5.4)
Mental status changes [l]	12 (15.2)	21 (17.1)	33 (16.3)
Insomnia	11 (13.9)	19 (15.4)	30 (14.9)
Renal and urinary disorders			
Renal impairment [m]	4 (5.1)	6 (4.9)	10 (5)
Respiratory, thoracic and mediastinal disorders			
Cough [n]	13 (16.5)	20 (16.3)	33 (16.3)
Dyspnea [o]	22 (27.8)	26 (21.1)	48 (23.8)
Epistaxis	10 (12.7)	15 (12.2)	25 (12.4)
Skin and subcutaneous tissues			
Alopecia	4 (5.1)	2 (1.6)	6 (3)
Vascular disorders			
Hypertension	4 (5.1)	3 (2.4)	7 (3.5)

[a] Includes terms sinus tachycardia, supraventricular tachycardia, and tachycardia
[b] Includes terms abdominal pain, abdominal pain upper, and abdominal pain lower
[c] Includes terms fatigue and asthenia
[d] Includes terms influenza and H1N1 influenza
[e] Includes terms pneumonia, atypical pneumonia, pneumocystis jirovecii pneumonia, pneumonia influenzal, and pneumonia viral
[f] Includes terms sepsis, staphylococcal sepsis, fungal sepsis, and septic shock
[g] Includes terms respiratory tract infection, upper respiratory tract infection, and lower respiratory tract infection
[h] Includes terms cervical vertebral fracture, clavicle fracture, compression fracture, femur fracture, hip fracture, humerus fracture, jaw fracture, lower limb fracture, rib fracture, sternal fracture, upper limb fracture, and pathological fracture
[i] Include terms hypercreatininemia and hypercreatinemia
[j] Includes terms hyperuricemia and blood uric acid increased
[k] Includes terms neuropathy peripheral, peripheral sensory neuropathy, and polyneuropathy
[l] Includes terms mental status changes, confusional state, and delirium
[m] Includes terms renal impairment, acute kidney injury, and renal injury
[n] Includes terms cough and productive cough
[o] Includes terms dyspnea, dyspnea at rest, and dyspnea exertional
(Source: FDA Analysis)

Laboratory Findings

For standard clinical laboratory test results, the Applicant provided shift tables presenting changes from baseline to worst on-study and baseline to last on-study values relative to NCI-CTCAE classification ranges. For certain key laboratory parameters (e.g., sodium, creatinine, platelets, hemoglobin, WBC, BUN-to-creatinine ratio, and urea-to-creatinine ratio), the Applicant also provided box plots and by-patient plots for measurements over time.

The Applicant noted the following observations with respect to laboratory findings in the primary safety population (Module 5.3.5.2 KCP-330-012 Study Report Body Section 12.4):

- Shifts from baseline to Grade 3 or 4 for hematology parameters included anemia (45.6%), leukopenia (35.6%), lymphopenia (42.5%), neutropenia (31.1%), and thrombocytopenia (67.5%)

- Shifts from baseline to Grade 3 or 4 for chemistry parameters that occurred in at least 3 patients included hyponatremia (30.5%), hyperglycemia (12.1%), hypophosphatemia (9.4%), hypokalemia (8.0%), creatinine increased (7.5%), elevated lipase (4.9%), hyperkalemia (3.0%), hypocalcemia (2.7%), and ALT increased (2.5%)

- No patients met criteria for Hy's Law

- There were no clinically significant urinalysis findings

Vital Signs

Potentially clinically significant post-baseline systolic blood pressure (SBP) elevations, defined as SBP ≥ 160 mmHg, were observed in 19 (9.4%) patients in the primary safety population. Hypertension was reported as an adverse event in 7 (3.5%) of patients and was Grade ≥ 3 in 2 (1%) patients. Potentially clinically significant post-baseline SBP decreases, defined as SBP < 90 mmHg, were observed in 8 (4%) patients in the primary safety population. Hypotension reported as an adverse event in 8 (4%) patients. Grade ≥ 3 hypotension was reported in 2 (1%) patients. Potentially clinically significant post-baseline diastolic blood pressure (DBP) increases, defined as DBP ≥100 mmHg, were observed in 9 (4.5%) patients in the primary safety population.

Potentially clinically significant post-baseline heart rate (HR) increases, defined as HR >120 bpm, were observed in 13 (6.4%) patients in the primary safety population. Potentially clinically significant post-baseline heart rate (HR) decreases, defined as HR <50 bpm, were observed in 3 (1.5%) patients in the primary safety population.

Electrocardiograms (ECGs)

Standard 12-lead ECGs were performed at screening and end-of-treatment. ECGs were interpreted by the Investigator and categorized as normal, abnormal but not clinically significant, or abnormal and clinically significant. The Applicant reported that 3 patients (1.5%) had baseline ECG results that were abnormal and clinically significant, 4 patients (5.6%) had worst on-study post-baseline ECGs that were abnormal and clinically significant, and 4 patients had last on-study post-baseline ECGs that were abnormal and clinically significant.

QT

The Interdisciplinary Review Team (IRT) for QT studies was consulted to review the submitted QT data. The IRT reviewed data from studies KCP-330-001 and KCP-330-003. The highest dose evaluated in these studies was 80 mg/m^2, which exceeds the recommended dosing of 80 mg (~45 mg/m^2) twice weekly. Exposure-response analysis suggested a trend of positive relationship between the change in QTcF and selinexor. Although no large QTc prolongation effect (i.e., >20 ms) of selinexor was observed, a smaller mean effect (i.e., 10 ms) cannot be ruled out in the absence of a placebo or positive control arm.

7.4.5 Updated Safety Results following Major Amendment

Following discussion with the FDA at a Post-ODAC Meeting on March 11, 2019, the Applicant submitted a major amendment to NDA 212306 on March 13, 2019.

Given concerns regarding the risk-benefit profile of XPOVIO in the originally proposed patient population, the Applicant revised the proposed indication to include a narrower population of patients with RRMM who are more heavily pretreated and whose disease is more refractory. Support for the revised indication is based on the results from a subpopulation of 83 patients from Part 2 of STORM who had received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors (PIs), at least two immunomodulatory agents (IMiDs), and an anti-CD38 monoclonal antibody. This population is referred to as the BCLPD-R (bortezomib-, carfilzomib-, lenalidomide-, pomalidomide-, daratumumab-refractory) population.

Updated safety analyses evaluating the revised patient population were conducted on the complete datasets provided by the Applicant for the STORM trial, which used a data cut-off date of April 24, 2018 at the time of the initial NDA submission and the updated adverse event dataset (adae2.xpt) submitted by the Applicant on February 5, 2019. The updated analyses also utilize a revised grouping of preferred terms (see Appendix), which is consistent with the grouping of preferred terms in the revised proposed prescribing information.

An overview of the safety results for the updated patient population from STORM is shown in Table 49. All patients in the BCLPD-R subpopulation experienced at least one TEAE, and the rates of severe (Grade 3-4) TEAEs, SAEs, TEAEs leading to permanent discontinuation of study treatment, and fatal TEAEs in the subpopulation did not differ from the overall population.

Table 49: Overview of TEAEs in BCLPD-Refractory Subpopulation

AE Category	BCLPD-R (N = 83) n (%)	Total (N = 202) n (%)
Any TEAE	83 (100)	202 (100)
Any Grade 3 or 4 TEAE	78 (94)	190 (94.1)
Serious TEAE	49 (59)	118 (58.4)
Discontinuation due to TEAE	23 (27.7)	54 (26.7)
Fatal TEAE	7 (8.4)	18 (8.9)

(Source: FDA Analysis)

Deaths

There were 42 (20.8%) deaths on or within 30 days of study treatment in STORM (N=202). Of these 42 deaths, 15 (18.1%) deaths occurred in patients in the BCLPD-refractory (BLCPD-R) population (N=83). Of these 15 deaths, 8 (9.6%) were due to disease progression and 7 (8.4%) were due to a fatal TEAE (Table 50). The causes of the 7 deaths due to a fatal TEAE were cardiac disorder, respiratory arrest, pneumonia (2 cases), sepsis, fungal sepsis, and subdural hematoma.

Table 50: Deaths in BCLPD-Refractory Subpopulation

Reason for Death	BCLPD-R (N = 83) n (%)	Total (N = 202) n (%)
All causes	15 (18.1)	42 (20.8)
Disease progression	8 (9.6) *	22 (10.9) *
TEAE	7 (8.4)	18 (8.9)
Insufficient information	0	2 (0.5)

*Reason for death for patient (b) (6) updated from "unknown" to "progressive disease" after data cut-off
(Source: FDA Analysis)

Serious Adverse Events

SAEs occurred in 58.4% of patients overall and 59% of patients in the BCLPD-R population. SAEs that occurred in at least 2% of patients overall or within the BCLPD-R subgroup are shown in Table 51. The most common SAEs in the BCLPD-R subpopulation (occurring in at least 5% of patients) were sepsis (9.6%), pneumonia (9.6%), mental status changes (8.4%), and fatigue (6%).

Table 51: SAEs in BCLPD-Refractory Subpopulation

System Organ Class Preferred Term*	**BCLPD-R (N = 83) n (%)**	**Total (N = 202) n (%)**
Blood and lymphatic system disorders		
Anemia	3 (3.6)	6 (3)
Thrombocytopenia	2 (2.4)	8 (4)
Gastrointestinal disorders		
Diarrhea	1 (1.2)	5 (2.5)
Nausea	0	5 (2.5)
General disorders and administration site conditions		
Fatigue	5 (6)	9 (4.5)
General physical health deterioration	1 (1.2)	4 (2)
Pyrexia	2 (2.4)	6 (3)
Infections and infestations		
Bacteremia	4 (4.8)	6 (3)
Influenza	1 (1.2)	6 (3)
Pneumonia	8 (9.6)	19 (9.4)
Sepsis	8 (9.6)	12 (5.9)
Upper respiratory tract infection	1 (1.2)	6 (3)
Injury, poisoning and procedural complications		
Fracture	1 (1.2)	8 (4)
Fall	0	4 (2)
Metabolism and nutrition disorders		
Dehydration	2 (2.4)	6 (3)
Hypercalcemia	0	4 (2)
Hyponatremia	3 (3.6)	5 (2.5)
Psychiatric disorders		
Mental status changes	7 (8.4)	13 (6.4)
Renal and urinary disorders		
Acute kidney injury	2 (2.4)	7 (3.5)

Respiratory, thoracic and mediastinal disorders Respiratory failure	1 (1.2)	4 (2)

*Includes grouped preferred terms (see Appendix 13.4)
(Source: FDA Analysis)

Dropouts and/or Discontinuations Due to Adverse Effects

Overall, 89.1% of patients in STORM had a dose interruption, dose reduction, or permanent discontinuation of study treatment due to a TEAE (Table 52).

Table 52: Dose Modifications Due to TEAEs in BCLPD-Refractory Subpopulation

Action Taken with Selinexor	BCLPD-R (N = 83) n (%)	Total (N = 202) n (%)
Dose modification due to TEAE	73 (88)	180 (89.1)
Dose reduced	38 (45.8)	87 (43.1)
Dose interrupted	59 (71.1)	140 (69.3)
Treatment permanently discontinued	23 (27.7)	54 (26.7)

(Source: FDA Analysis (ADAE2 Dataset))

TEAEs led to dose reduction in 43.1% of patients in STORM overall, and 45.8% of patients in the BCLPD-R subpopulation. The TEAEs leading to dose reduction in at least 2% of patients overall or in the BCLPD-R subpopulation are summarized in Table 53.

Table 53: TEAEs Leading to Dose Reduction in BCLPD-Refractory Subpopulation

System Organ Class Preferred Term*	BCLPD-R (N = 83) n (%)	Total (N = 202) n (%)
Blood and lymphatic system disorders		
Neutropenia	7 (8.4)	7 (3.5)
Thrombocytopenia	26 (31.3)	60 (29.7)
Gastrointestinal disorders		
Nausea	11 (13.3)	11 (5.4)
Vomiting	3 (3.6)	3 (1.5)
General disorders and administration site conditions		
Fatigue	5 (6)	13 (6.4)
General physical health deterioration	2 (2.4)	2 (1)

Investigations		
Weight decreased	7 (8.4)	7 (3.5)
Metabolism and nutrition disorders		
Decreased appetite	4 (4.8)	4 (2)
Dehydration	2 (2.4)	2 (1)
Hyponatremia	3 (3.6)	3 (1.5)
Psychiatric disorders		
Mental status changes	1 (1.2)	5 (2.5)

*Includes grouped preferred terms (see Appendix 13.4)
(Source: FDA Analysis (ADAE2 Dataset))

TEAEs led to dose interruption in 69.3% of patients in STORM overall, and 71.1% of patients in the BCLPD-R subpopulation. The TEAEs leading to dose reduction in at least 2% of patients overall or in the BCLPD-R subpopulation are summarized in Table 54.

Table 54: TEAEs Leading to Dose Interruption in BCLPD-Refractory Subpopulation

System Organ Class Preferred Term*	**BCLPD-R (N = 83) n (%)**	**Total (N = 202) n (%)**
Blood and lymphatic system disorders		
Anemia	5 (6)	11 (5.4)
Leukopenia	3 (3.6)	3 (1.5)
Neutropenia	7 (8.4)	11 (5.4)
Thrombocytopenia	23 (27.7)	56 (27.7)
Gastrointestinal disorders		
Diarrhea	1 (1.2)	4 (2)
Nausea	5 (6)	12 (5.9)
Vomiting	4 (4.8)	12 (5.9)
General disorders and administration site conditions		
Fatigue	12 (14.5)	25 (12.4)
Pyrexia	2 (2.4)	6 (3)
Infections and infestations		
Pneumonia	4 (4.8)	12 (5.9)
Sepsis	2 (2.4)	3 (1.5)
Upper respiratory tract infection	3 (3.6)	11 (5.4)
Injury, poisoning and procedural complications		
Fracture	0	5 (2.5)

Investigations Weight decreased	3 (3.6)	7 (3.5)
Metabolism and nutrition disorders Decreased appetite Hyponatremia	3 (3.6) 5 (6)	9 (4.5) 14 (6.9)
Nervous system disorders Cognitive disorder Peripheral sensory neuropathy	2 (2.4) 2 (2.4)	2 (1) 2 (1)
Psychiatric disorders Mental status changes	2 (2.4)	6 (3)
Renal and urinary disorders Acute kidney injury	2 (2.4)	6 (3)
Uncoded Uncoded	2 (2.4)	2 (1)

*Includes grouped preferred terms (see Appendix 13.4)
(Source: FDA Analysis (ADAE2 Dataset))

TEAEs led to permanent discontinuation of study treatment in 26.7% of patients in STORM overall, and 27.7% of patients in the BCLPD-R subpopulation. The TEAEs leading to permanent discontinuation in at least 2% of patients overall or in the BCLPD-R subpopulation are summarized in Table 55.

Table 55: TEAEs Leading to Permanent Discontinuation in BCLPD-Refractory Subpopulation

System Organ Class Preferred Term*	**BCLPD-R (N = 83) n (%)**	**Total (N = 202) n (%)**
Blood and lymphatic system disorders Anemia Thrombocytopenia	1 (1.2) 1 (1.2)	4 (2) 8 (4)
Gastrointestinal disorders Diarrhea Nausea Vomiting	2 (2.4) 4 (4.8) 1 (1.2)	4 (2) 10 (5) 4 (2)
General disorders and administration site conditions Fatigue	7 (8.4)	14 (6.9)

Infections and infestations Pneumonia	4 (4.8)	5 (2.5)
Investigations Weight decreased	2 (2.4)	6 (3)
Metabolism and nutrition disorders Decreased appetite	2 (1.2)	5 (2.5)
Psychiatric disorders Mental status changes	2 (2.4)	5 (2.5)

*Includes grouped preferred terms (see Appendix 13.4)
(Source: FDA Analysis (ADAE2 Dataset))

TEAEs leading to any dose modification (reduction, interruption, or permanent discontinuation) in the overall population and BCLPD-R subpopulation are summarized by system organ class in Table 56.

Table 56: TEAEs Leading to Dose Modification in BCLPD-Refractory Subpopulation by System Organ Class

System Organ Class	BCLPD-R (N = 83) n (%)	Total (N = 202) n (%)
Blood and lymphatic system disorders	40 (48.2)	103 (51)
Cardiac disorders	1 (1.2)	1 (0.5)
Ear and labyrinth disorders	0	2 (1)
Eye disorders	0	2 (1)
Gastrointestinal disorders	17 (20.5)	46 (22.8)
General disorders and administration site conditions	21 (25.3)	51 (25.2)
Infections and infestations	16 (19.3)	43 (21.3)
Injury, poisoning and procedural complications	5 (6)	7 (3.5)
Investigations	6 (7.2)	23 (11.4)
Metabolism and nutrition disorders	13 (15.7)	43 (21.3)
Musculoskeletal and connective tissue disorders	2 (2.4)	3 (1.5)
Neoplasms benign, malignant and unspecified	0	1 (0.5)
Nervous system disorders	9 (10.8)	14 (6.9)

Psychiatric disorders	6 (7.2)	14 (6.9)
Renal and urinary disorders	4 (4.8)	10 (5)
Respiratory, thoracic and mediastinal disorders	5 (6)	14 (6.9)
Skin and subcutaneous tissue disorders	1 (1.2)	2 (1)
Surgical and medical procedures	0	1 (0.5)
Uncoded	2 (2.4)	2 (1)
Vascular disorders	1 (1.2)	1 (0.5)

(Source: FDA Analysis (ADAE2 Dataset))

Significant Adverse Events

Approximately 94% of patients in both the overall STORM population and the BCLPD-R subpopulation experienced at least one severe (Grade 3-4) TEAE. Severe TEAEs that occurred in at least 5% of patients overall are summarized in Table 57. The most common severe TEAEs (occurring in at least 10% of patients) in the BCLPD-R subpopulation were anemia (44.6%), leukopenia (15.7%), lymphopenia (10.8%), neutropenia (24.1%), thrombocytopenia (59%), nausea (10.8%), fatigue (25.3%), and hyponatremia (21.7%).

Table 57: Grade 3 or 4 TEAEs in BCLPD-Refractory Subpopulation

System Organ Class Preferred Term*	**BCLPD-R Grades 3-4 (N = 83) n (%)**	**Total Grades 3-4 (N = 202) n (%)**
Blood and lymphatic system disorders		
Anemia	37 (44.6)	81 (40.1)
Leukopenia	13 (15.7)	23 (11.4)
Lymphopenia	9 (10.8)	20 (9.9)
Neutropenia	20 (24.1)	43 (21.3)
Thrombocytopenia	49 (59)	124 (61.4)
Gastrointestinal disorders		
Diarrhea	7 (8.4)	13 (6.4)
Nausea	9 (10.8)	18 (8.9)
General disorders and administration site conditions		
Fatigue	21 (25.3)	44 (21.8)
Infections and infestations		
Pneumonia	5 (6)	18 (8.9)
Sepsis	7 (8.4)	13 (6.4)
Metabolism and nutrition disorders		
Hyperglycemia	4 (4.8)	15 (7.4)
Hyponatremia	18 (21.7)	44 (21.8)
Psychiatric disorders		
Mental status changes	6 (7.2)	14 (6.9)

*Includes grouped preferred terms (see Appendix 13.4)
(Source: FDA Analysis)

Treatment Emergent Adverse Events and Adverse Reactions

All patients in STORM experienced at least one TEAE. The most common TEAEs of any grade that occurred in at least 10% of patients in STORM overall or in the BCLPD-R subpopulation are shown in Table 58. The most common TEAEs (occurring in at least 20% of patients) in the BCLPD-R subpopulation were anemia (66.3%), leukopenia (33.7%), neutropenia (42.2%), thrombocytopenia (73.5%), constipation (22.9%), diarrhea (45.8%), nausea (66.3%), vomiting (36.1%), fatigue (67.5%), upper respiratory tract infection (20.5%), weight decreased (44.6%), decreased appetite (55.4%), hypokalemia (20.5%), hyponatremia (36.1%), mental status changes (20.5%), and dyspnea (21.7%).

Table 58: TEAEs in BCLPD-Refractory Subpopulation

System Organ Class Preferred Term*	**BCLPD-R** **All Grades** **(N = 83)** **n (%)**	**Total** **All Grades** **(N = 202)** **n (%)**
Blood and lymphatic system disorders		
Anemia	55 (66.3)	119 (58.9)
Leukopenia	28 (33.7)	57 (28.2)
Lymphopenia	12 (14.5)	30 (14.9)
Neutropenia	35 (42.2)	68 (33.7)
Thrombocytopenia	61 (73.5)	149 (73.8)
Eye disorders		
Vision blurred	10 (12)	21 (10.4)
Gastrointestinal disorders		
Abdominal pain	9 (10.8)	18 (8.9)
Constipation	19 (22.9)	50 (24.8)
Diarrhea	38 (45.8)	89 (44.1)
Nausea	55 (66.3)	146 (72.3)
Vomiting	30 (36.1)	82 (40.6)
General disorders and administration site conditions		
Fatigue	56 (67.5)	147 (72.8)
Peripheral edema	10 (12)	16 (7.9)
Pyrexia	15 (18.1)	32 (15.8)
Infections and infestations		
Pneumonia	12 (14.5)	26 (12.9)
Sepsis	9 (10.8)	13 (6.4)
Upper respiratory tract infection	17 (20.5)	42 (20.8)
Investigations		
Weight decreased	37 (44.6)	95 (47)
Metabolism and nutrition disorders		
Decreased appetite	46 (55.4)	108 (53.5)
Dehydration	5 (6)	28 (13.9)
Hypercreatininemia	10 (12)	28 (13.9)
Hyperglycemia	8 (9.6)	31 (15.3)
Hypocalcemia	10 (12)	19 (9.4)
Hypokalemia	17 (20.5)	25 (12.4)
Hyponatremia	30 (36.1)	78 (38.6)

Nervous system disorders		
Dizziness	15 (18.1)	30 (14.9)
Dysgeusia	9 (10.8)	22 (10.9)
Psychiatric disorders		
Insomnia	14 (16.9)	30 (14.9)
Mental status changes	17 (20.5)	33 (16.3)
Respiratory, thoracic and mediastinal disorders		
Cough	10 (12)	33 (16.3)
Dyspnea	18 (21.7)	48 (23.8)
Epistaxis	8 (9.6)	25 (12.4)

*Includes grouped preferred terms (see Appendix 13.4)
(Source: FDA Analysis)

Reviewer Comment: The frequency, types, and severity of TEAEs in the BCLPD-R subpopulation was similar to what was observed in the overall population in STORM.

7.4.6 Analysis of Submission-Specific Safety Issues

The following safety issues were identified as warranting more thorough evaluation: thrombocytopenia, neutropenia, gastrointestinal toxicity, hyponatremia, infections, and neurological toxicity.

Thrombocytopenia

A total of 149 (73.8%) patients in STORM (N=202) experienced at least one TEAE of thrombocytopenia (including preferred terms thrombocytopenia and platelet count decreased). Of these 149 patients, 124 (61.4%) had at least one episode of severe (Grade 3-4) thrombocytopenia, and 8 (4%) had an SAE of thrombocytopenia. Concurrent thrombocytopenia and bleeding (bleeding events identified by analysis dataset flag "HEMORRFL") occurred in 37 (18.3%) patients, and 6 (3%) patients had thrombocytopenia with severe (Grade 3-4) bleeding. These events included Grade 3 epistaxis in patient (b) (6) Grade 5 (fatal) subdural hematoma in patient (b) (6), Grade 3 rectal hemorrhage in patients (b) (6) and (b) (6), Grade 3 hematoma in patients (b) (6), and Grade 3 procedural hemorrhage (2 episodes) in patient (b) (6)

Neutropenia

Neutropenia occurred in 68 (33.7%) patients in STORM and 43 (21.3%) patients had at least one episode of severe (Grade 3-4) neutropenia. Febrile neutropenia occurred in 5 (2.5%) patients. Of the 43 patients who experienced severe neutropenia, 29 (67.4%) received G-CSF (filgrastim or pegfilgrastim) as a concomitant medication.

Gastrointestinal Toxicity

TEAEs classified under the system organ class heading of gastrointestinal disorders occurred in 186 (92.1%) patients in STORM and 39 (19.3%) patients experienced at least one severe (Grade 3-4) gastrointestinal TEAE. A total of 173 (85.6%) patients experienced at least one event of diarrhea, nausea, or vomiting and 30 (14.9%) patients had at least one severe event.

A total of 89 (44.1%) patients experienced at least one episode of diarrhea, and 24 (11.9%) experienced recurrent diarrhea. Diarrhea was mild to moderate (Grade 1-2) in severity in the majority (85.4%) of patients and only 13 (6.4%) patients experienced severe (Grade 3) diarrhea. Dose interruption due to diarrhea was required in 4 (2%) patients, and 4 (2%) patients permanently discontinued study treatment due to diarrhea.

A total of 146 (72.3%) patients had at least one episode of nausea, 65 (32.2%) had recurrent nausea, and 18 (8.9%) experienced severe (Grade 3) nausea. Dose interruption due to nausea was required in 12 (5.9%) patients, 11 (5.4%) patients had a dose reduction due to nausea, and 10 (5%) patients permanently discontinued study treatment due to nausea.

A total of 82 (40.1%) patients had at least one episode of vomiting, 24 (11.9%) had recurrent vomiting, and 7 (3.5%) had severe (Grade 3) vomiting. Dose interruption due to vomiting was required in 12 (5.9%) patients, 3 (1.5%) patients had a dose reduction due to vomiting, and 4 (2%) patients permanently discontinued study treatment due to vomiting.

Hyponatremia

In NCI-CTCAE (version 4.03), Grade 1 hyponatremia is defined as a sodium level between 130 mmol/L and the lower limit of normal, Grade 3 hyponatremia is defined as a sodium level between 120 – 130 mmol/L, and Grade 4 hyponatremia is defined as a sodium level less than 120 mmol/L (Grade 2 hyponatremia does not exist in this grading scale). In STORM, 78 (38.6%) of patients experienced hyponatremia of any grade. A total of 34 (16.8%) patients had Grade 1 hyponatremia, 42 (20.8%) patients had Grade 3 hyponatremia, and 2 (1%) patients developed Grade 4 hyponatremia. Dose interruption due to hyponatremia was required in 14 (6.9%) patients, and 3 (1.5%) patients had a dose reduction due to hyponatremia.

Infections

Infections of any type and grade (identified by system organ class heading Infections and Infestations) occurred in 105 (52%) patients. Grade 3-4 (severe) infections occurred in 47 (23.3%) of patients, and fatal (Grade 5) infections (including influenza, pneumonia, sepsis, fungal sepsis, and septic shock) occurred in 7 (3.5%) patients. Infections of any grade that occurred in at least 2% of patients included upper respiratory tract infection (20.8%), pneumonia (12.9%), sepsis (6.4%), influenza (4.5%), urinary tract infection (4.5%), sinusitis (3.5%), fungal skin infection (2%), and cellulitis (2%).

Neurological Toxicity

Neurological toxicities, including dizziness, syncope, depressed level of consciousness, delirium, confusional state, and mental status changes occurred in 61 (30.2%) patients in STORM. A total of 19 (9.4%) patients had at least one severe (Grade 3-4) episode of neurological toxicity.

7.4.7 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

7.4.8 Safety Analyses by Demographic Subgroups

Of the 202 patients enrolled and treated in STORM, 97 (48.1%) patients were aged 65 and above, and 23 (11.4%) patients were aged 75 and above.

In the age 65 years and above subpopulation, there were no remarkable differences in the incidences of TEAEs (Table 59).

Table 59: Overview of TEAEs in Patients Aged 65 and Above

AE Category	Age ≥65 (N = 97) n (%)	Total (N = 202) n (%)
Any TEAE	97 (100)	202 (100)
Any Grade 3 or 4 TEAE	89 (91.8)	190 (94.1)
Serious TEAE	58 (59.8)	118 (58.4)
Discontinuation due to TEAE	28 (28.9)	54 (26.7)
Fatal TEAE	9 (9.3)	18 (8.9)

(Source: FDA Analysis)

In patients aged 75 years and above, although fewer patients in this subgroup had Grade 3-4 TEAEs (82.6% vs. 94.1%), they experienced higher incidences of SAEs (69.6% vs. 58.4%), permanent discontinuation of study treatment due to TEAEs (43.5% vs. 26.7%), and fatal TEAEs (17.4% vs. 8.9%) (Table 60).

Table 60: Overview of TEAEs in Patients Aged 75 and Above

AE Category	Age ≥75 (N = 23) n (%)	Total (N = 202) n (%)
Any TEAE	23 (100)	202 (100)
Any Grade 3 or 4 TEAE	19 (82.6)	190 (94.1)
Serious TEAE	16 (69.6)	118 (58.4)
Discontinuation due to TEAE	10 (43.5)	54 (26.7)
Fatal TEAE	4 (17.4)	18 (8.9)

(Source: FDA Analysis)

Reviewer Comment: A higher incidence of SAEs, discontinuations due to TEAEs, and fatal TEAEs was observed in patients aged 75 and above. This information will be incorporated into the selinexor prescribing information.

STORM included 35 (17.3%) patients who were black or African American. All patients had at least one TEAE; however, the rates of severe TEAEs and SAEs were nearly the same as the overall population, and there was a trend towards decreased rates of permanent discontinuation of study treatment due to TEAEs and fatal TEAEs in this subgroup (Table 61).

Table 61: Overview of TEAEs in Black/African American Patients

AE Category	Black/African American (N = 35) n (%)	Total (N = 202) n (%)
Any TEAE	35 (100)	202 (100)
Any Grade 3 or 4 TEAE	33 (94.3)	190 (94.1)
Serious TEAE	21 (60)	118 (58.4)
Discontinuation due to TEAE	6 (17.1)	54 (26.7)
Fatal TEAE	2 (5.7)	18 (8.9)

(Source: FDA Analysis)

Reviewer Comment: The types and severity of TEAEs in Black/African American patients did not differ substantially from the overall population in STORM.

7.4.9 Specific Safety Studies/Clinical Trials

Pooled Safety Analyses

Safety analyses included safety data pooled from studies KCP-330-001, KCP-330-008, KCP-330-009, KCP-330-010, KCP-330-012, and KCP-330-013 (Pool 1 – all studies of single-agent selinexor +/- dexamethasone in patients with hematological malignancies, Table 62), and from studies KCP-330-001, KCP-330-012, KCP-330-017, and KCP-330-023 (Pool 2 – all patients with MM, Table 63). Refer to Table 13 for further details about these clinical trials.

Table 62: Study Populations Included in Pool 1 (Patients with Hematological Malignancies)

Study	All HM	MM	AML[a]	Non-MM, non-AML HM[a]
KCP-330-001 (HM)	All dosed patients	All dosed patients with MM	All dosed patients with AML	All dosed patients not including MM and AML
KCP-330-008 (AML)	All dosed patients	Not applicable	All dosed patients	Not applicable
KCP-330-009 (DLBCL)	All dosed patients	Not applicable	Not applicable	All dosed patients
KCP-330-010 (Richter's)	All dosed patients	Not applicable	Not applicable	All dosed patients
KCP-330-012 (STORM) (MM)	All dosed patients	All dosed patients	Not applicable	Not applicable
KCP-330-013 (PTCL/CTCL)	All dosed patients	Not applicable	Not applicable	All dosed patients

AML: acute myeloid leukemia; CTCL: cutaneous T-cell lymphoma; DLBCL: diffuse large B-cell lymphoma; HM: hematological malignancies; MM: multiple myeloma; PTCL: peripheral T-cell lymphoma.
(Source: Applicant's Summary of Clinical Safety, Module 2.7.4, Table 4)

Table 63: Study Populations Included in Pool 2 (All Patients with MM)

Study	All MM	MM S (80 mg)+d	MM Other S±d	MM S (QW)+Vd[a]	MM S (BIW)+Vd[a]	MM SRd[a]	MM SPd[a]	MM SDd[a]
KCP-330-001	All dosed patients with MM	All patients with MM dosed with S (80 mg or 45 mg/m^2) +d	All patients with MM dosed with a regimen other than S (80 mg) +d	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
KCP-330-012/ STORM	All dosed patients	All dosed patients	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
KCP-330-017	All dosed patients	Not applicable	Not applicable	All dosed patients assigned to a QW cohort of SVd arm	All dosed patients assigned to BIW cohort of SVd arm	All dosed patients assigned to SRd arm	All dosed patients assigned to SPd arm	All dosed patients assigned to SDd arm
KCP-330-023/ BOSTON	All patients dosed with SVd	Not applicable	One patient who crossed over from Vd to Sd	All patients dosed with SVd	Not applicable	Not applicable	Not applicable	Not applicable

BIW: twice weekly; D: daratumumab; d: dexamethasone; MM: multiple myeloma; P: pomalidomide; QW: once weekly; R: lenalidomide; S: selinexor; V: bortezomib.
(Source: Applicant's Summary of Clinical Safety, Module 2.7.4, Table 5)

Safety data from Pools 1 and 2 were combined for analysis of TEAEs, SAEs, and fatal TEAEs. In total, there were 1116 patients in the pooled safety analysis population (962 patients in Pool 1 and 437 patients in Pool 2, with some patients with MM overlapping between the two pools).

The Applicant reported the following regarding the pooled safety data:

- Non-hematological TEAEs occurring in ≥25% of patients were nausea (63%), fatigue (57.2%), decreased appetite (52.3%), diarrhea (38.4%), vomiting (34.8%), decreased weight (30.1%), hyponatremia (27.4%), and constipation (25.9%)
- Hematological TEAEs occurring in ≥25% of patients were thrombocytopenia (54.7%), anemia (42.6%), and neutropenia (28.9%)
- SAEs occurring in ≥5% of patients were pneumonia (9.4%), febrile neutropenia (7.5%), and sepsis (6.7%)
- A total of 172 (15.4%) of patients had a fatal TEAE; fatal TEAEs occurring in ≥0.5% of patients were pneumonia (2.8%), sepsis (2.8%), febrile neutropenia (0.8%), respiratory failure (0.8%), general physical health deterioration (0.6%), lung infection (0.6%), and multiple organ dysfunction syndrome (0.6%)

Reviewer Comment: The results of the pooled safety analysis are similar to the findings in STORM and the pooled analysis did not identify any new safety signals.

Safety Update

The Summary of Clinical Safety (Module 2.7.4) of the new drug application (NDA 212306) was submitted on 05 August 2018. The original submission summarized the clinical data in the Summary of Clinical Safety (SCS) based on a data cut-off date of April 24, 2018 for STORM, and a data cut-off date of March 31, 2018 for the ongoing studies KCP-330-009, KCP-330-017, and KCP-330-023 (BOSTON). The data cut-off date for the 90-day safety update was August 17,

2018. The update included safety data from 149 new patients, including 115 patients with MM, treated with selinexor in studies KCP-330-009, KCP-330-017, and BOSTON. Updated data for Pools 1 and 2 was also included.

The Applicant reported the following observations regarding the updated safety data:

- Non-hematologic TEAEs occurring in ≥25% of patients in Pool 2 were nausea, fatigue, decreased appetite, decreased weight, diarrhea, vomiting, hyponatremia, and dyspnea
- Hematologic TEAEs occurring in ≥25% of patients in Pool 2 were thrombocytopenia, anemia, neutropenia, and leukopenia
- 16 patients in Pool 1 had a new SAE; the most common SAEs among all patients in Pool 1 were pneumonia (8.9%), febrile neutropenia (7.9%), and sepsis (7.1%)
- 33 patients in Pool 2 had a new SAE; pneumonia is the only SAE that occurred in ≥5% of patients in Pool 2
- TEAEs leading to permanent discontinuation of selinexor occurred in 16 additional patients in Pool 1 and 9 additional patients in Pool 2
- 5 patients had new fatal TEAEs (strangulated hernia and pulmonary embolism in Pool 1 and 2, and hemorrhagic shock, myocardial infarction, and sepsis in Pool 2

Reviewer Comment: No new safety signals for selinexor plus dexamethasone were identified in the 90-day safety update.

7.4.10 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Carcinogenicity studies were not conducted to support the use of selinexor for the proposed indication. Refer also to section 5.5.3.

Human Reproduction and Pregnancy

There has not been exposure to selinexor in pregnant or lactating women. Based on the mechanism of action of selinexor and findings from animal studies, selinexor is associated with a potential risk for embryo-fetal toxicity.

Pediatrics and Assessment of Effects on Growth

There has not been exposure to selinexor in pediatric patients.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Experience with overdose of selinexor is very limited. One patient (b) (6) in STORM experienced a TEAE of Grade 2 overdose. At the beginning of study treatment, the patient received selinexor 80 mg and dexamethasone 20 mg on Days 1 and 3, as planned; however, due

to misunderstanding, the patient also received selinexor 80 mg on Days 5 and 7. On study Day 8, the patient was hospitalized due to an SAE of Grade 3 tumor lysis syndrome and was discovered to also have an SAE of Grade 2 overdose. Both events resolved by Day 13. The patient resumed treatment with selinexor on Day 15 and was discharged home on Day 19.

There is no abuse potential for this product.

7.4.11 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Selinexor is not marketed in any country.

Expectations on Safety in the Postmarket Setting

APPEARS THIS WAY ON ORIGINAL

It is not expected that the safety of selinexor in combination with dexamethasone will differ in the postmarket setting from that observed in clinical trials in the patient population proposed in the indication.

7.4.12 Integrated Assessment of Safety

The safety of selinexor in combination with dexamethasone was evaluated in detail in 202 patients with RRMM who were assigned to receive selinexor 80 mg in combination with dexamethasone 20 mg twice weekly on Days 1 and 3 in the STORM trial. Safety was also assessed in pooled datasets that included a total of 1116 patients with hematologic malignancies, including 437 patients with MM who received treatment with selinexor alone, in combination with dexamethasone, or in combination with other agents. The key safety results are as follows:

- A total of 42 deaths (20.8%) occurred on or within 30 days of study treatment in STORM; of the 42 deaths, 18 (8.9%) were due to a fatal TEAE, 22 (10.9%) were due to disease progression, and 2 (0.5%, both in Part 1) were attributed to disease progression by the Applicant but had insufficient information to support attribution to progressive disease.
- All patients (100%) in STORM had at least one TEAE, 94.1% of patients had at least one severe (Grade 3-4) TEAE, 58.4% of patients had at least one SAE, 26.7% of patients permanently discontinued study treatment due to a TEAE, and 8.9% of patients had a fatal TEAE.
- SAEs that occurred in at least 5% of patients overall were: pneumonia (8.4%), sepsis (5.9%), and mental status changes (6.4%).
- Grade 3-4 TEAEs that occurred in at least 10% of patients overall were: anemia (40.1%), leukopenia (11.4%), neutropenia (21.3%), thrombocytopenia (61.4%), fatigue (21.8%), and hyponatremia (21.8%).
- TEAEs of any grade that occurred in at least 20% of patients overall were: anemia (58.9%), leukopenia (28.2%), neutropenia (33.7%), thrombocytopenia (73.8%), constipation (24.8%), diarrhea (44.1%), nausea (72.3%), vomiting (40.6%), fatigue (72.8%), upper respiratory tract infection (20.8%), weight decreased (47%), decreased appetite (53.5%), hyponatremia (38.6%), and dyspnea (23.8%)
- Most patients (89.1%) required at least one dose modification due to TEAEs; 43.1% of patients required at least one dose reduction due to a TEAE, 69.3% of patients required at least one dose interruption due to a TEAE, and 26.7% of patients permanently discontinued study treatment due to a TEAE.
- TEAEs that led to discontinuation in at least 2.5% of patients overall were: thrombocytopenia (4%), nausea (5%), fatigue (6.9%), weight decreased (3%), decreased appetite (2.5%), and mental status changes (2.5%).
- Compared to the overall population, the percentages and types of severe TEAEs, SAEs, discontinuation due to TEAEs and fatal TEAEs were similar within the Part 2 and BCLDP-

R populations.

- Compared to younger patients in the overall population, patients 75 years and above had higher incidences of SAEs (69.6% vs. 58.4%), permanent discontinuation of study treatment due to TEAEs (43.5% vs. 26.7%), and fatal TEAEs (17.4% vs. 8.9%).
- No new safety signals arose from the pooled safety datasets or 90-day safety update.

7.5 SUMMARY AND CONCLUSIONS

7.5.1 Conclusions and Recommendations

The efficacy of selinexor in combination with dexamethasone was established based on ORR, supported by DOR. The ORR for the mITT population consisting of 122 patients treated with selinexor plus dexamethasone in Part 2 of STORM was 25.4%, with a median DOR of 4.4 months. The magnitude and duration of response is potentially meaningful for patients with RRMM if the toxicity profile is acceptable. However, treatment with selinexor is associated with significant toxicity, and it has a unique toxicity profile compared to other approved agents for the treatment of RRMM. In addition, STORM was a single-arm trial evaluating the combination of selinexor and dexamethasone. The trial design does not isolate the treatment effect of selinexor, and selinexor did not demonstrate single agent activity in RRMM in the phase 1 trial. Furthermore, patients required dose modifications early in the trial and a substantial proportion (26.8%) of patients in Part 2 discontinued study treatment due to an adverse event. The median duration on treatment at the proposed dose of selinexor 80 mg in combination with dexamethasone 20 mg twice weekly was only 3.5 weeks, suggesting that the proposed starting dose was poorly tolerated. Lower doses of selinexor in combination with dexamethasone were not evaluated in the phase 1 trial, and therefore, it is not clear whether the optimal dose of selinexor in combination with dexamethasone has been identified for patients with MM. Lastly, single arm trials do not allow for a full assessment of safety due to lack of a comparator arm and challenges in ascertaining the baseline rates of adverse events in a population of patients with advanced MM.

Given the toxicity profile of selinexor, the indication was revised to include only those patients who have received at least four prior lines of therapy, and whose disease is refractory to at least two PIs, at least two IMiDs, and an anti-CD38 mAb. This represents a population who for all intents and purposes has no available therapy, and therefore, the benefit-risk profile of selinexor is acceptable in this population.

The review team recommends accelerated approval for selinexor. The endpoint of ORR reflects a short-term benefit, and long-term outcomes for the treatment of patients with RRMM with selinexor in combination with dexamethasone are not currently available. Additional information from a randomized, phase 3 confirmatory trial is needed to confirm the clinical benefit of selinexor in patients with MM.

The ongoing BOSTON trial of selinexor in combination with bortezomib and dexamethasone compared to bortezomib and dexamethasone alone will serve as the confirmatory trial and was issued as a post-marketing requirement (PMR). Other PMRs include the conduct of a randomized phase 2 trial to characterize the safety and efficacy of at least 2 doses of selinexor, conduct of a hepatic impairment trial, and conduct of a dedicated drug interaction trial.

Primary Statistical Reviewer	Statistical Team Leader
Primary Clinical Reviewer	Clinical Team Leader

8 Advisory Committee Meeting and Other External Consultations

The Application was presented to the Oncologic Drug Advisory Committee (ODAC) on February 26, 2019. FDA requested discussion of whether the KCP-330-012 (STORM) data are conclusive to allow for an adequate assessment of the safety and efficacy in the proposed patient population, and whether selinexor provides a benefit that outweighs the risks.

The specific issues presented to the ODAC are as follows:

Single Arm Trial of a Combination: STORM was a single arm trial evaluating the combination of selinexor and dexamethasone. Given that historical studies have shown response rates of 10-27% to high-dose dexamethasone for RRMM and selinexor did not demonstrate single agent activity in RRMM in the phase 1 trial KCP-330-001, it is difficult to isolate the treatment effect of selinexor.

Toxicity: Treatment with selinexor is associated with significant toxicity. In Part 2 of STORM, all patients (100%) experienced at least one TEAE, nearly two-thirds (60.2%) of patients experienced an SAE, most patients (91.1%) required a dose modification due to a TEAE and over a one-quarter (26.8%) of patients discontinued treatment with selinexor-dexamethasone due to a TEAE. In the absence of a control arm, it can be challenging to interpret safety results. In study KCP-330-008, a randomized-controlled trial of selinexor versus physician's choice conducted in patients with AML, there was worse overall survival in the selinexor arm, highlighting the toxicity of this drug.

Dose Selection: As a monotherapy, selinexor yielded only one response (PR) in 56 patients with RRMM in the phase 1 dose escalation and expansion study KCP-330-001. The proposed starting dose of selinexor 80 mg orally in combination with dexamethasone 20 mg orally on Days 1 and 3 of each week with or without food was based on data obtained from the phase 1 trial that included cohorts evaluating two dose levels of selinexor, 45 mg/m^2 (approximately equivalent to 80 mg) or 60 mg/m^2 (approximately equivalent to 100 mg), in combination with dexamethasone 20 mg on days 1 and 3 of each week in patients with RRMM. The 45 mg/m^2 dose was better tolerated than the 60 mg/m^2 dose. However, the Applicant did not evaluate selinexor doses lower than 45 mg/m^2 in combination with dexamethasone 20 mg at the proposed dosing schedule in trial KCP-330-001. The proposed starting dose was not well tolerated in the phase 2 trial given that 91.1% the patients in Part 2 of STORM required at least one dose modification due to a TEAE and 26.8% of patients discontinued treatment with selinexor-dexamethasone due to a TEAE. Exposure-response analyses indicate a relationship between higher exposures and adverse events, suggesting that lower doses of selinexor may be better tolerated.

The voting question was "Should the approval of selinexor be delayed until results of the

randomized phase 3 trial, KCP-330-023 (BOSTON), are available?" The final vote was 8 votes Yes, 5 votes No.

9 Pediatrics

The Applicant was granted Orphan Designation for selinexor for the treatment of patients with MM and is therefore exempt from pediatric studies under the Pediatric Research Equity Act (PREA). There is no data regarding the use of selinexor in pediatric patients.

10 Labeling Recommendations

10.1 Prescription Drug Labeling

Labeling negotiations were ongoing at the time of this review. The proposed labeling information submitted by the Applicant required substantial revisions. The recommended major changes to the selinexor prescribing information proposed by the Applicant are summarized below:

Section 1 Indications and Usage: The indication statement was revised to reflect a more refractory population.

Section 2 Dosage and Administration: The recommended safety monitoring was revised to recommend more frequent monitoring during the first two months of treatment. The dosage reduction steps and modification guidelines for adverse reactions were revised to make the recommendations simpler and clearer for prescribers and to provide appropriate recommendations for dose modifications.

Section 5 Warnings and Precautions: The warnings and precautions (W&P) were reordered, revised to include additional W&P. The content of the W&P was revised to include clinically useful and accurate information.

Section 6 Adverse Reactions: The adverse reactions table was revised to group clinically related preferred terms and combine rates of Grade 3 and higher adverse reactions.

Section 8 Use in Specific Populations: The Geriatric Use section was revised to indicate differences in safety for the population of patients 75 years of age and above.

Section 14 Clinical Studies: This section was revised to reflect the revised indication and include a description that the approval is based upon efficacy and safety in the subgroup of 83 patients from STORM Part 2. The section was revised to remove (b) (4)

10.2 Patient Labeling

Review of patient labeling by the Division of Medical Policy Programs in the Office of Medical Policy is ongoing.

A Medication Guide was not initially included in the prescribing information by the Applicant, but was requested by the FDA to convey the risks for adverse reactions with selinexor treatment, and the importance of early communication with the healthcare provider if the patients notes any new or concerning side effects.

11 Risk Evaluation and Mitigation Strategies (REMS)

The risks of selinexor can be adequately managed in the post-marketing setting through product presentation and labeling. The Division of Risk Management in the Office of Surveillance and Epidemiology reviewed this Application and concurs that no additional risk evaluation and management strategies are recommended.

12 Postmarketing Requirements and Commitment

One clinical trial to evaluate treatment of patients with RRMM with selinexor in a randomized setting will be required under FDAAA:

PMR-1: Complete and submit a final report with full datasets from the ongoing multicenter, randomized, controlled, phase 3 clinical trial (KCP-330-023) comparing selinexor in combination with bortezomib and dexamethasone (SVd) to bortezomib and dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy. The primary objective is to compare progression free survival (PFS) in both treatment arms.

Trial Completion: 3/2020
Final Report Submission: 9/2020

The following three pharmacokinetic clinical studies will be required under FDAAA:

PMR-2: Conduct a randomized phase 2 clinical trial of selinexor in combination with dexamethasone to characterize the safety and efficacy of at least two different doses of selinexor, which are lower than the dosing regimen of 80 mg on Days 1 and 3 of each week, in patients with relapsed refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody. The primary objective is to assess the overall response rate in all treatment arms according to International Myeloma Working Group (IMWG) criteria by investigator assessment. The trial should include one interim analysis for futility. The results of this trial will be used to inform the optimal dose for selinexor in this patient population. Submit a final report with full datasets.

Preliminary Protocol Submission to Include SAP: 08/2019
Final Protocol Submission: 10/2019
Interim Analysis: 12/2020
Trial Completion: 06/2021
Final Report Submission: 10/2021

PMR-3: Conduct a hepatic impairment trial in patients with NCI classification of moderate, severe hepatic impairment or Child-Pugh classes B, and C compared to patients with normal hepatic function since drug clearance may be reduced with hepatic impairment.

Preliminary Protocol Submission: 08/2019
Final Protocol Submission: 09/2019
Trial Completion: 03/2021

Final Report Submission: 09/2021

PMR-4: Conduct a drug interaction trial in patients to evaluate the effect of co-administration of a strong CYP3A4 inhibitor on the pharmacokinetics of selinexor.

Preliminary Protocol Submission: 08/2019
Final Protocol Submission: 09/2019
Trial Completion: 03/2021
Final Report Submission: 09/2021

The following post-marketing commitment will also be issued:

PMC-1: Conduct a dedicated drug interaction trial in patients to determine the effect of co administration of a strong CYP3A4 inducer on the pharmacokinetics of selinexor.

Preliminary Protocol Submission: 09/2020
Final Protocol Submission: 03/2021
Trial Completion: 03/2022
Final Report Submission: 09/2022

Division Director (DHOT)

Division Director (OCP)

Division Director (OB)

Division Director (Clinical)

Multiple myeloma remains an incurable disease with an associated mortality. Selinexor is a first in class agent. Selinexor's efficacy (response rate) was demonstrated in a single arm trial where all patients also received dexamethasone. Dexamethasone is part of many treatment regimens for multiple myeloma and has single agent activity. Selinexor has minimal if any single agent activity based on the submitted data. However, the combination of selinexor and dexamethasone appears at least synergistic in the single arm trial due to the higher than expected response rate if due to dexamethasone alone. Patients experienced significant toxicity particularly for metabolic, gastrointestinal toxicities, hematologic, neurologic, anorexia/weight loss, neurological toxicities, and infection. Although questions remain about clinical benefit, dosing and how best to manage toxicities I concur with the recommendation of the clinical team for approval. Labeling will include warnings, dose modification guidelines and concomitant medication recommendations to allow for the safe administration of selinexor. Post-marketing requirements include a confirmatory trial to verify the clinical benefit of selinexor in patients with multiple myeloma, a randomized phase 2 trial to characterize the safety and efficacy of lower doses of selinexor, a hepatic impairment trial, and a dedicated drug interaction trial.

Ann T. Farrell, MD

Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

13 Appendices

13.1 References

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13.2 Financial Disclosure

Covered Clinical Study (Name and/or Number): KCP-330-012 (STORM)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 65		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0		

Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3 OCP Appendices (Technical documents supporting OCP recommendations)

13.3.1 Summary of Bioanalytical Method Validation and Performance

Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Yes, plasma concentrations of the active parent selinexor (KPT-330) and its trans-isomer (KPT-375) were measured in the clinical pharmacology and biopharmaceutics studies. KPT-375 was the most abundant metabolite in plasma. Plasma KPT-375 concentrations were low when compared to selinexor, with mean Cmax values less than 5% of those achieved for parent drug in all dose groups. There was no accumulation for both selinexor and KPT-375 after multiple doses. Circulating metabolites have limited contribution to clinical efficacy and safety.

Selinexor was extensively metabolized with parent drug accounting for less than 5% in feces or urine. Qualified methods were developed to measure selinexor and KPT-375 concentrations in urine and feces. There is no understanding of how much metabolites in feces and urine represent administered dose given there is no human ADME study data.

For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The total plasma concentration of selinexor was measured in the clinical trials. This was appropriate due to the constant plasma protein binding of selinexor over the clinically relevant concentration range studied. The average binding of selinexor to proteins in human plasma was around 95% across concentration range from 0.1 to 10 μM.

What bioanalytical methods are used to assess concentrations?

Two LC-MS/MS methods were developed to quantify selinexor and KPT-375 in plasma (TRTPR12-039 and 0096-1191). Di-potassium ethylenediaminetetraacetic acid was used as the anticoagulant. The method involves protein precipitation extraction followed by LC-MS/MS analysis employing an internal standard (KPT-330-d5 in isopropanol) of selinexor. The assay was validated to a lower limit of quantitation (LLOQ) of 1.00 ng/mL using 0.050 mL of plasma and a linear range of 1.00 to 1000 ng/mL. Selinexor was stable in acidified plasma for 928 days at -80°C. A listing of the bioanalytical methods used in each of the studies is provided in Table 64. In addition to the studies listed on the Table, LC-MS/MS method 0096-1191 were used in study KCP-330-008, KCP-330-012

LC-MS/MS methods were developed to quantify selinexor and KPT-375 in urine (0096-1320) and feces (0096-1400).

Table 64: Analytical Methods and Assay Validation Reports of Selinexor and KPT-375 in Human Plasma in Clinical Studies

Validation Report	Clinical Studies Supported	Method Description	Performance	
TRTPR12-039, TRTPR12-039A1, TRTPR12-039A2	KCP-330-001 KCP-330-002	An aliquot of human plasma containing the analyte and internal standard (KPT-330-D_5) was extracted using a protein precipitation extraction procedure. The extracted samples were analyzed by an HPLC equipped with an AB/MDS SCIEX API 4000 mass spectrometer.	Standard Concentrations (ng/mL)	1.00, 2.00, 10.0, 80.0, 200, 500, 800, 1000
			Linear Range (ng/mL)	1.00 to 1000
			Recovery (%)	101.4 to 104.8
			Coefficient of Determination (R^2)	0.9971
			LLOQ (ng/mL)	1.00
			Intra-Run Precision (% CV) at LLOQ	1.9 to 3.0
			Intra-Run Accuracy (% difference from theoretical) at LLOQ	-3.6 to 11.0
			Inter-Run Precision (% CV) at LLOQ	6.0
			Inter-Run Accuracy (% bias) at LLOQ	2.0
			QC Concentrations (ng/mL)	LLOQ: 1.00 ng/mL Low: 3.00 ng/mL Low-Mid: 40.0 ng/mL Mid: 400 ng/mL High: 750 ng/mL Dil QC: 10,000 ng/mL

Validation Report	Clinical Studies Supported	Method Description	Performance	
			Intra-Run Precision (% CV) of QC Samples	1.00 ng/mL: 1.9 to 3.0 3.00 ng/mL: 1.5 to 5.2 40.0 ng/mL: 1.3 to 3.0 400 ng/mL: 1.4 to 2.6 750 ng/mL: 1.1 to 3.1 10,000 ng/mL: 1.6 to 3.4
			Intra-Run Accuracy (% difference from theoretical) of QC Samples	1.00 ng/mL: -3.6 to 11.0 3.00 ng/mL: 0.0 to 6.3 40.0 ng/mL: -2.0 to 5.0 400 ng/mL: -4.3 to 1.5 750 ng/mL: -6.1 to -2.8 10,000 ng/mL: -2.9 to 3.0
			Inter-Run Precision (% CV) of QC Samples	LLOQ: 6.0 Low: 3.7 Low-Mid: 2.9 Mid: 2.7 High: 2.8 Dil QC: 2.9
			Inter-Run Accuracy (% difference from theoretical) of QC Samples	LLOQ: 2.0 Low: 4.0 Low-Mid: 2.3 Mid: -1.8 High: -4.3 Dil QC: -0.8
			Hemolysis Evaluation	No effect from hemolysis on quantitation
			Freeze/Thaw Stability	4 cycles (3.00 and 750 ng/mL) at -70°C
			Bench Top Stability	14 h (3.00 and 750 ng/mL) on ice
			Extract Stability	97 h (3.00, 400, and 750 ng/mL) at 1 to 8°C
			Reinjection Reproducibility	116 h (3.00, 400, and 750 ng/mL) at 1 to 8°C
			Whole Blood Stability	2 h at room temperature and 1 to 8°C
			Long-Term Matrix Stability	23 d at -20°C and 518 d at -70°C (3.00 and 750 ng/mL)
			Long-Term Stock Solution Stability (prepared in 90% DMSO:10% water)	74 d at -20°C
			Bench Top Stock Solution Stability (prepared in 90% DMSO:10% water)	48 h at room temperature
			Bench Top ISWS Stability	16 h on ice

Validation Report	Clinical Studies Supported	Method Description	Performance	
0096-1191, 0096-1191.02, 0096-1191.03	KCP-330-010 KCP-330-003	An aliquot of human plasma containing the analyte and internal standard (KPT-330-D_5) was extracted using a protein precipitation extraction procedure. The extracted samples were analyzed by a Waters Acquity UPLC™ liquid chromatograph equipped with a Thermo Scientific TSQ Vantage triple quadrupole mass spectrometer.	Standard Concentrations (ng/mL)	1.00, 2.00, 10.0, 50.0, 100, 400, 800, 1000
			Linear Range (ng/mL)	1.00 to 1000
			Recovery (%)	121.9 to 124.4
			Coefficient of Determination (R^2)	0.9995 to 0.9996
			LLOQ (ng/mL)	1.00
			Intra-Run Precision (% CV) at LLOQ	2.2 to 5.1
			Intra-Run Accuracy (% bias) at LLOQ	-0.2 to 11
			Inter-Run Precision (% CV) at LLOQ	3.7
			Inter-Run Accuracy (% bias) at LLOQ	7
			QC Concentrations (ng/mL)	Low QC: 3.00 ng/mL Middle QC: 75.0 ng/mL High QC: 750 ng/mL Over-range: 5000 ng/mL
			Intra-Run Precision (% CV) of QC Samples	3.00 ng/mL: 1 to 3.4 75.0 ng/mL: 0.8 to 2.6 750 ng/mL: 1 to 1.4 5000 ng/mL: 1.3
			Intra-Run Accuracy (% bias) of QC Samples	3.00 ng/mL: -8.7 to 12 75.0 ng/mL: -5.5 to 10.4 750 ng/mL: -2.9 to 6.8 5000 ng/mL: -2.8
			Hemolysis Evaluation	Hemolysis can yield a significant negative bias on the quantitation of selinexor
			Freeze/Thaw Stability	4 cycles (3.00 and 750 ng/mL) at -20 and -80°C
			Bench Top Stability	6 h (3.00 and 750 ng/mL) on wet ice
			Extract Stability	55 h (3.00 and 750 ng/mL) at 2 to 8°C
			Reinjection Reproducibility	19 h (3.00 and 750 ng/mL) at 2 to 8°C
			Whole Blood Stability	Inconclusive[a]
			Long-Term Matrix Stability (acidified plasma)	928 d at -80°C and 93 days at -20°C (3.00 and 750 ng/mL)
			Stock Solution Stability	265 d at -10 to -30°C

CV: coefficient of variation; Dil: dilution; DMSO: dimethylsulfoxide; HPLC: high performance liquid chromatography; ISWS: internal standard working solution; KPT-330: selinexor; LC-MS/MS: liquid chromatography with tandem mass spectrometry; LLOQ: lower limit of quantitation; QC: quality control; UPLC: ultra performance liquid chromatography

[a] The trending and precision of whole blood stability did not meet acceptance criteria (%CV for each set was ≤15.0%, and the mean % change of each time group relative to the control group was within ± 15.0% for both concentrations. Some results showed drug concentrations increasing during the waiting period, compared to the control group, and other tests showed declining values. The tests were likely to have been impacted by hemolysis and analyte partitioning during experimental execution

(Source: Table 10 of Section 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods)

Table 65: Analytical Methods and Assay Validation Reports of Selinexor and KPT-375 in Urine and Feces in Clinical Studies

Qualified Report	Clinical Studies Supported	Method Description	Performance	
0096-1320	KCP-330-003	An aliquot of human urine containing the analyte and internal standard (KPT-330-D_5) was extracted using a protein precipitation extraction procedure. The extracted samples were analyzed by a Waters Acquity UPLC™ liquid chromatograph equipped with a Thermo Scientific TSQ Vantage triple quadrupole mass spectrometer.	Linear Range (ng/mL)	1.00 to 1000
			LLOQ (ng/mL)	1.00
			Intra-Run Precision (%CV) at LLOQ	3.3
			Intra-Run Accuracy (% bias) at LLOQ	-1.1
0096-1400	KCP-330-003	An aliquot of human feces containing the analyte and internal standard (KPT-330-D_5) was extracted using a protein precipitation extraction procedure. The extracted samples were analyzed by a Dionex UltiMate 3000 liquid chromatograph equipped with a Thermo Scientific TSQ Quantiva triple quadrupole mass spectrometer with ESI ionization.	Linear Range (ng/mL)	1.00 to 1000
			LLOQ (ng/mL)	1.00
			Intra-Run Precision (%CV) at LLOQ	3.9
			Intra-Run Accuracy (% bias) at LLOQ	2

CV: coefficient of variation; ESI: electro-spray ionization; UPLC: ultra performance liquid chromatography; LLOQ: lower limit of quantitation

(Source: Table 11 of Section 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods)

13.3.2 Clinical PK

Selinexor PK was not studied in healthy subjects. In patients with cancer, selinexor PK characteristics were evaluated after the first dose (Studies KCP-330-001, KCP-330-002, KCP-330-003) and after multiple doses (Studies KCP-330-001, KCP-330-002). The PK parameters after the first dose are summarized in Table 66. Only sparse PK data was collected in Study KCP-330-012 Part 1. The PK data in Study KCP-330-012 Part 1 were used for popPK model analysis. Following a single 80 mg (about 45 mg/m^2) dose in study 001, the mean Cmax and AUC is 680 ng/mL (about 1.5 µM) and 5386 ng•h/mL, respectively.

Table 66: Summary of Selinexor PK Parameters in Patients with Cancer After the First Dose

Study	Dose (N)	C_{max} (ng/mL)	AUC_{0-t} (ng•h/mL)
KCP-330-001	3 mg/m^2 (2)	51.2 (NA)	331 (NA)
KCP-330-002	3 mg/m^2 (1)	30 (NA)	333 (NA)
KCP-330-001	6 mg/m^2 (3)	55.0 (47.4)	593 (36.1)
KCP-330-002	6 mg/m^2 (3)	78 (32.4)	711 (13.5)
KCP-330-001	12 mg/m^2 (6)	159 (41.0)	1484 (19.8)
KCP-330-002	12 mg/m^2 (7)	155 (31.4)	1607 (20.6)
KCP-330-001	16.8 mg/m^2 (13)	222 (40.2)	1875 (23.4)
KCP-330-002	16.8 mg/m^2 (1)	168 (NA)	1369 (NA)
KCP-330-002	20 mg/m^2 (5)	237 (44.4)	2496 (21.5)
KCP-330-001	23 mg/m^2 (18)	277 (30.2)	2931 (32.4)
KCP-330-002	23 mg/m^2 (5)	310 (11.5)	3429 (17.6)
KCP-330-002	28 mg/m^2 (8)	329 (45.4)	3233 (30.3)

Study	Dose (N)	C_{max} (ng/mL)	AUC_{0-t} (ng•h/mL)
KCP-330-001	30 mg/m^2 (21)	408 (31.0)	3582 (27.9)
KCP-330-002	30 mg/m^2 (16)	456 (50.2)	3911 (16.7)
KCP-330-003	30 mg/m^2 (14) [a]	393 (44.0)	2913 (33.1)
KCP-330-003	30 mg/m^2 (14)[b]	429 (34.4)	3266 (24.1)
KCP-330-003	30 mg/m^2 (14)[c]	445 (20.0)	3336 (18.8)
KCP-330-003	30 mg/m^2 (14)[d]	445 (27.1)	3412 (21.1)
KCP-330-003	35 mg/m^2 (14)[e]	546 (32.3)	4173 (20.1)
KCP-330-003	35 mg/m^2 (13)[f]	550 (31.9)	4306 (19.5)
KCP-330-003	35 mg/m^2 (13)[g]	498 (43.5)	4029 (18.3)
KCP-330-001	35 mg/m^2 (13)	442 (42.5)	4053 (29.5)
KCP-330-002	35 mg/m^2 (10)	358 (22.9)	3793 (24.8)
KCP-330-002	39 mg/m^2 (4)	531 (12.4)	4930 (16.3)
KCP-330-001	40 mg/m^2 (8)	441 (39.1)	4593 (24.5)
KCP-330-002	40 mg/m^2 (6)	513 (63.8)	5379 (22.8)
KCP-330-002	45 mg/m^2 (3)	398 (24.4)	4476 (23.3)
KCP-330-001	46 mg/m^2 (9)	680 (18.2)	5335 (21.3)
KCP-330-002	50 mg/m^2 (4)	561 (49.1)	5492 (3.1)
KCP-330-001	55 mg/m^2 (8)	627 (42.7)	5921 (37.0)
KCP-330-002	55 mg/m^2 (3)	511 (18.1)	5904 (21.8)
KCP-330-002	58 mg/m^2 (4)	603 (44.0)	5965 (18.3)
KCP-330-001	60 mg/m^2 (4)	693 (29.1)	5781 (40.6)
KCP-330-002	65 mg/m^2 (7)	1059 (60.4)	9150 (41.4)
KCP-330-001	70 mg/m^2 (8)	832 (27.3)	5891 (37.7)
KCP-330-002	70 mg/m^2 (1)	521 (NA)	7210 (NA)
KCP-330-001	80 mg/m^2 (5)	1,175 (53.8)	5788 (34.1)
KCP-330-002	80 mg/m^2 (2)	766 (6.6)	9877 (12.6)
KCP-330-002	85 mg/m^2 (3)	1312 (31.7)	11642 (20.6)

[a] First generation tablet in a fasted state
[b] First generation tablet following consumption of a high-fat meal
[c] First generation tablet following consumption of a low-fat meal
[d] Capsule following consumption of a low-fat meal
[e] First generation tablet in a fed state
[f] Second generation tablet in a fed state
[g] Suspension prepared from the first generation tablets in a fed state

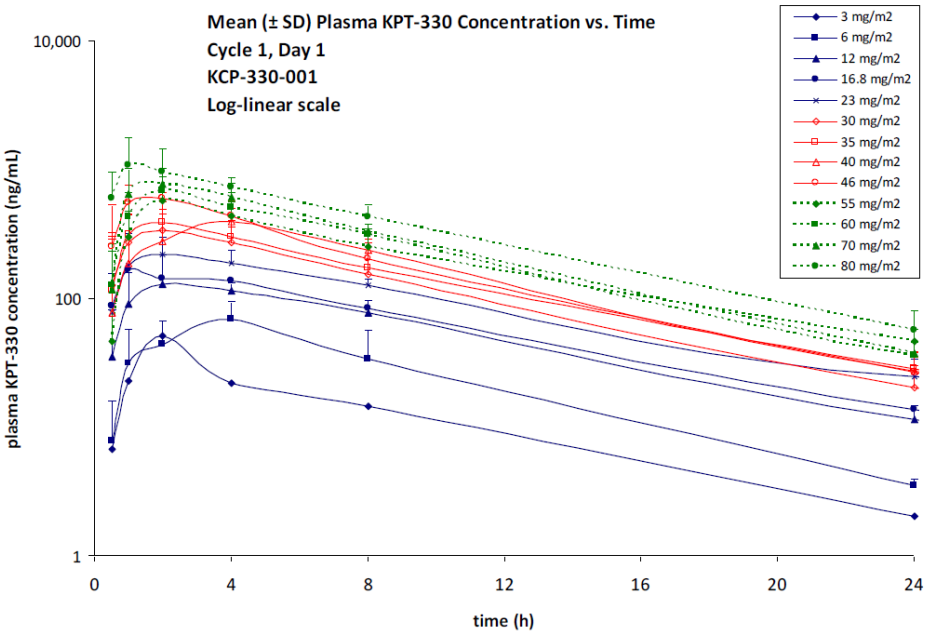
(Source: Table 8 of Section 2.7.2 Summary of Clinical Pharmacology Studies)

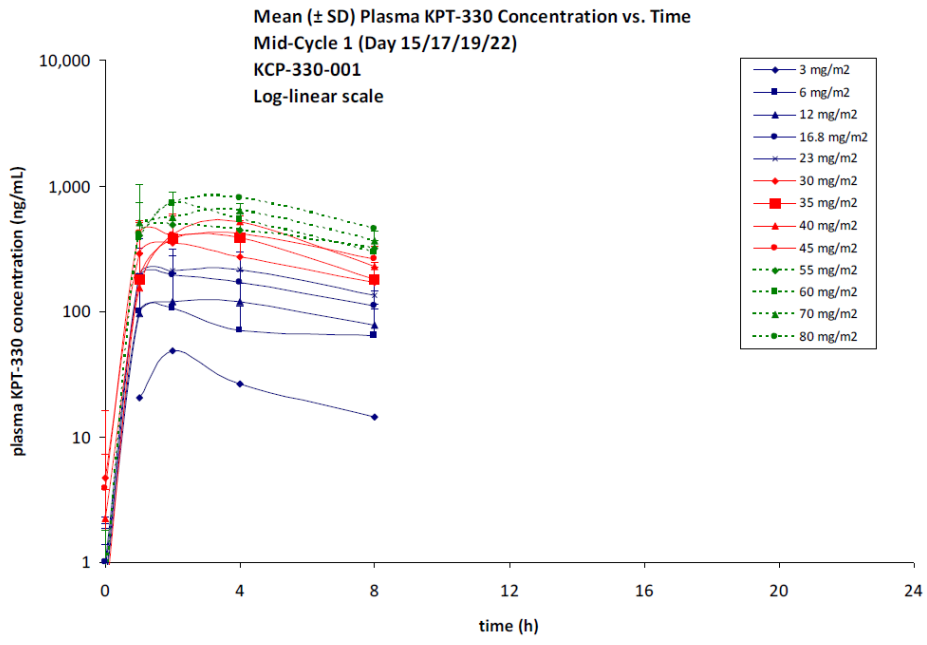
In Study KCP-330-001, selinexor plasma concentration vs time profiles were measured after a single dose and after multiple doses across the dose range of 3 to 80 mg/m^2 (Figure 11). There is no substantial accumulation following multiple doses for administration on days 1 and 3 of

each week (Figure 12). Plasma selinexor exposure was dose proportional across the 3 - 80 mg/m^2 dose range. Power model analyses of log-transformed selinexor Cmax and AUC_{inf} against log-transformed individual dose showed linear regressions consistent with dose proportionality, with slope values of 1.01 and 0.98, respectively (Figure 13).

Figure 11: Semi-logarithmic Mean (SD) Plasma Concentration vs. Time Profile of Selinexor (KPT-330)

(After a single (C1D1; upper figure) and multiple (C1D15/17/19/22; lower figure) twice weekly administration)

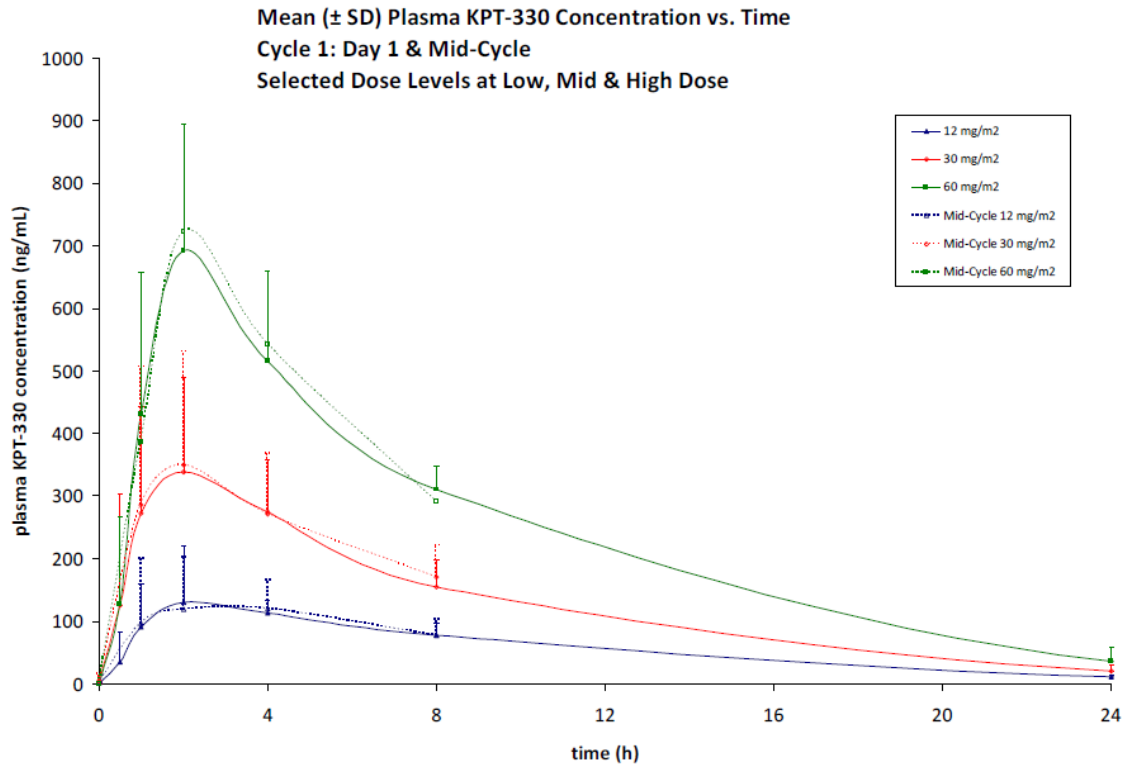




(Source: Figure 11 (upper figure) and Figure 12 (lower figure) of Section 5.3.4.2 KCP-330-001 Study Report Body)

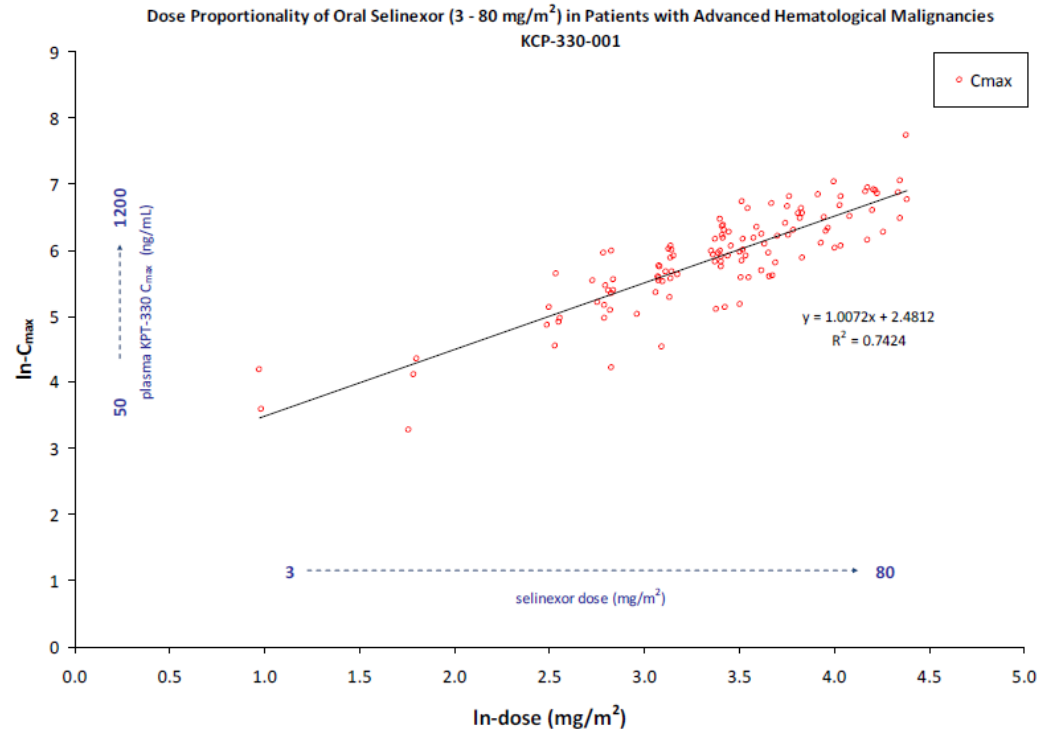
Figure 12: Semi-logarithmic Mean (SD) Plasma Concentration vs. Time Profile of Selinexor (KPT-330)

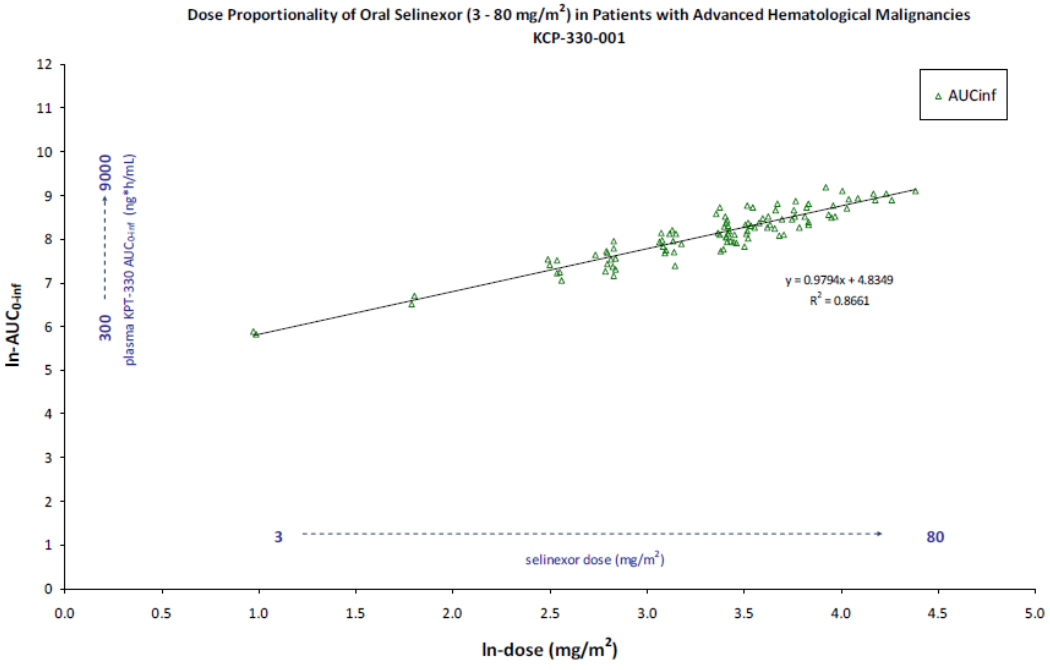
(After a single (C1D1; solid line) and multiple [mid-cycle (C1D15/17/19/22); dotted line] twice weekly administration)



(Source: Section 5.3.4.2 KCP-330-001 Study Report Body)

Figure 13: Dose Proportionality for Selinexor Cmax and AUC_{inf} PK Parameters at Cycle 1 Day 1





(Source: Figure 7.1.1 and 7.1.2 KCP-330-001: PK in Patients with Advanced Hematological Malignancies Section 5.3.5.2)

13.3.3 Exposure-Response Analyses

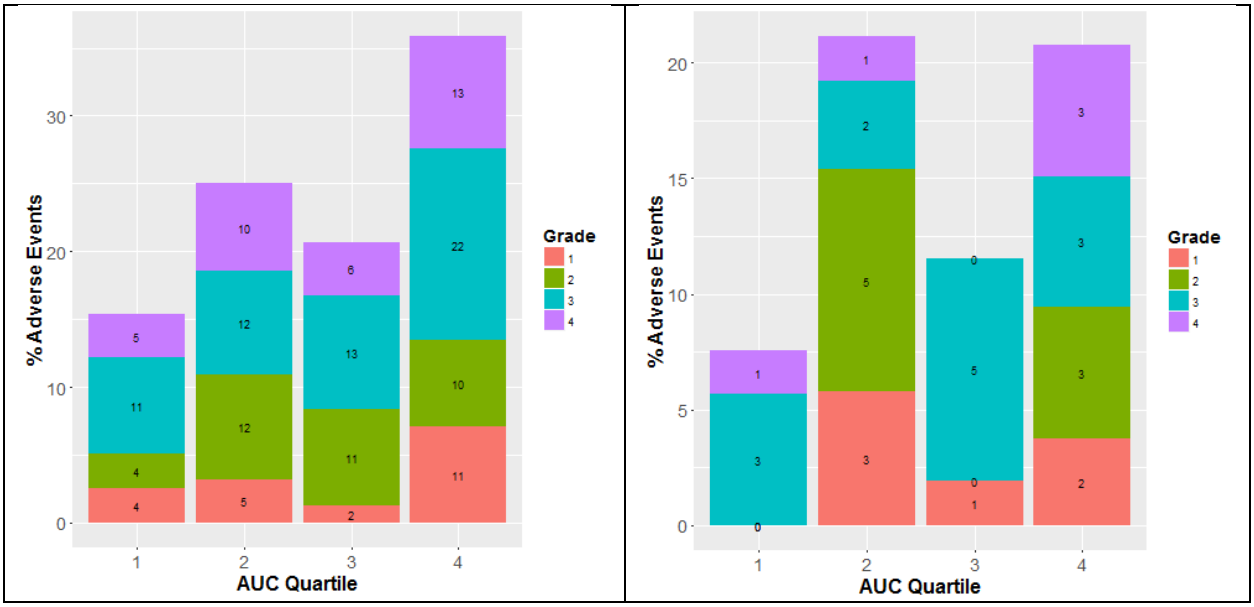
An independent exposure-response analysis for safety was conducted by the reviewer for the following adverse events from the ISS:

- AEDECOD = “Neutropenia” and “Neutrophil count decreased”
- AEDECOD = “Thrombocytopenia”
- AESOC = “Gastrointestinal disorders”
- AEDECOD = “Diarrhea”
- AEDECOD = “Vomiting”
- AEDECOD = “Decreased appetite”
- AEDECOD = “Weight decreased”
- AEDECOD = “Fatigue”
- AEDECOD = “Hyponatremia”
- AESOC = “Eye disorders”

This analysis was performed for both the full PK-safety dataset (N = 623 with PK from studies KCP-330-01, KCP-330-008, KCP-330-009, KCP-330-010, and KCP-330-012) and the MM patient set (N = 201 with PK from studies KCP-330-001 and KCP-330-012). The time to the first event of the respective category (e.g. thrombocytopenia) for the individual was determined and was utilized to calculate the dose intensity (cumulative dose to event/time to event). The dose intensity was then divided by the average clearance to give a ‘time-averaged’ AUC. The individuals were assigned a rank order based on these time-average AUCs and divided into four quartiles. The occurrence of the first events by AUC quartile were plotted in Figures 14–23 in a stacked bar chart, grouped by the toxicity grade for that first adverse event. For most of these plots, higher exposure indicated a higher rate of AEs. The results appeared similar between the two populations.

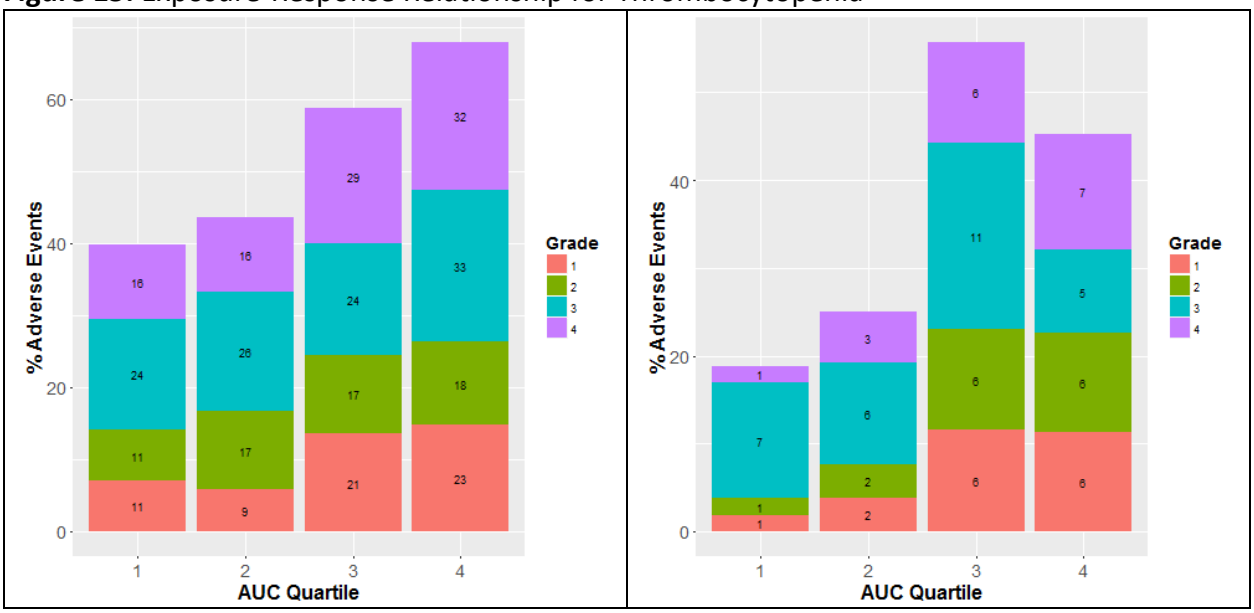
For each of the following graphs (Figure 14 to Figure 23), the y-axis is the percentage of subjects with the adverse event. The numbers in the plot indicate the number of individuals with that grade event in each AUC quartile. The grade of the adverse event refers to the grade at the first occurrence for that individual. The left panel represents the full PK-safety dataset while the right panel is the analysis for MM patients.

Figure 14: Exposure-Response Relationship for Neutropenia and Decreased Neutrophil Count



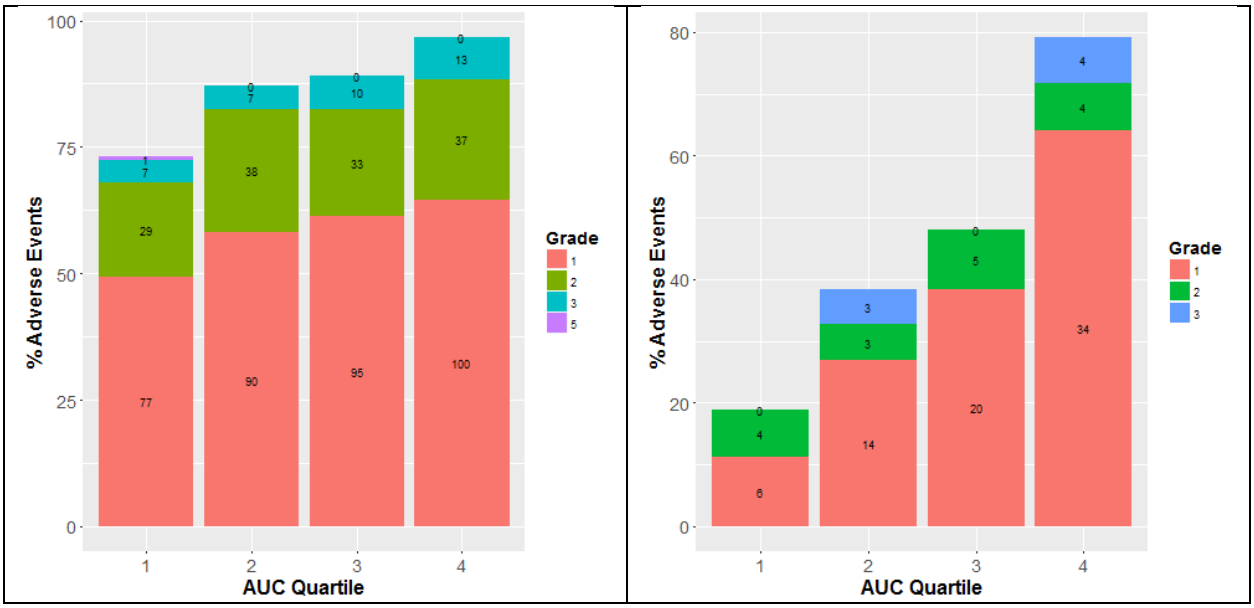
(Source: FDA Analysis)

Figure 15: Exposure-Response Relationship for Thrombocytopenia



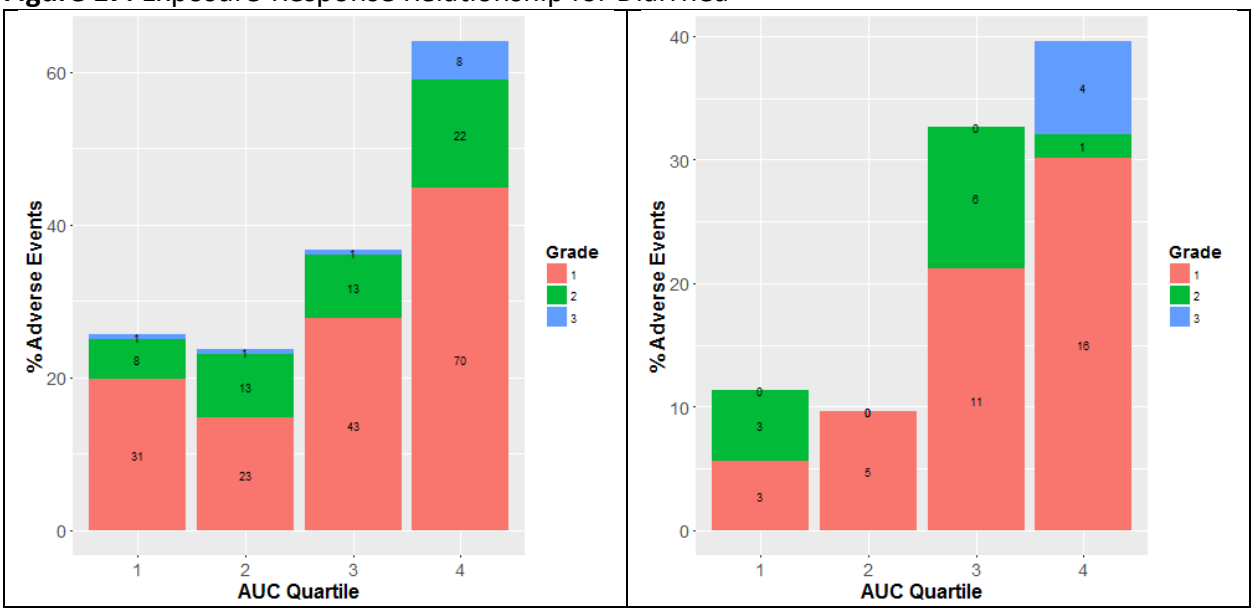
(Source: FDA Analysis)

Figure 16: Exposure-Response Relationship for Gastrointestinal Disorders



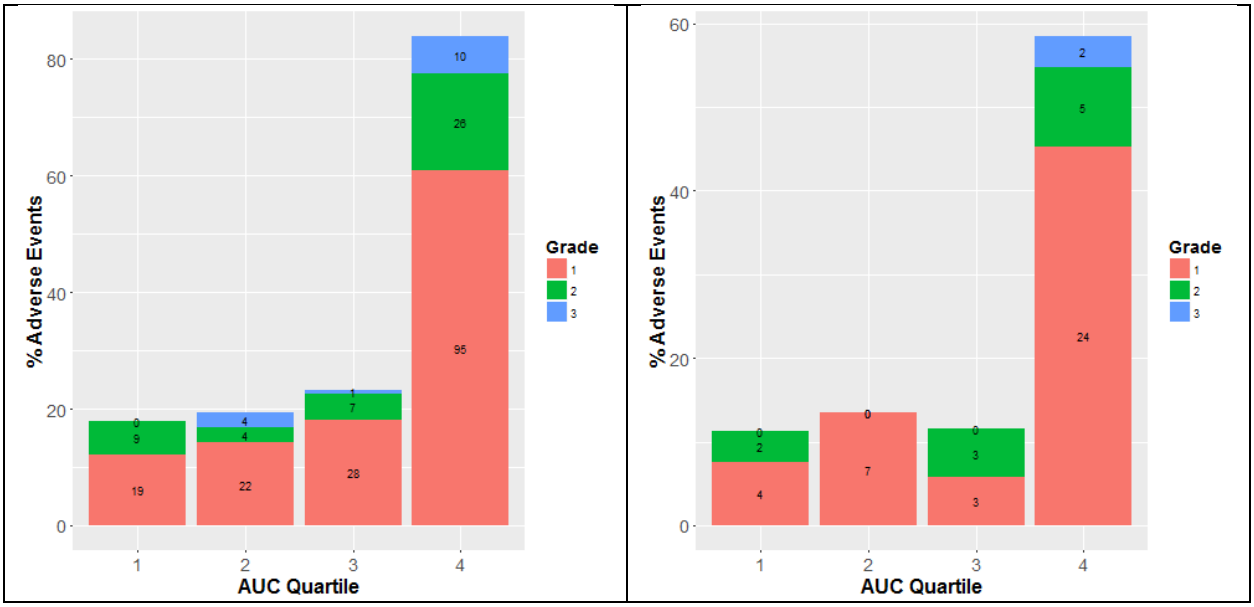
(Source: FDA Analysis)

Figure 17: Exposure-Response Relationship for Diarrhea



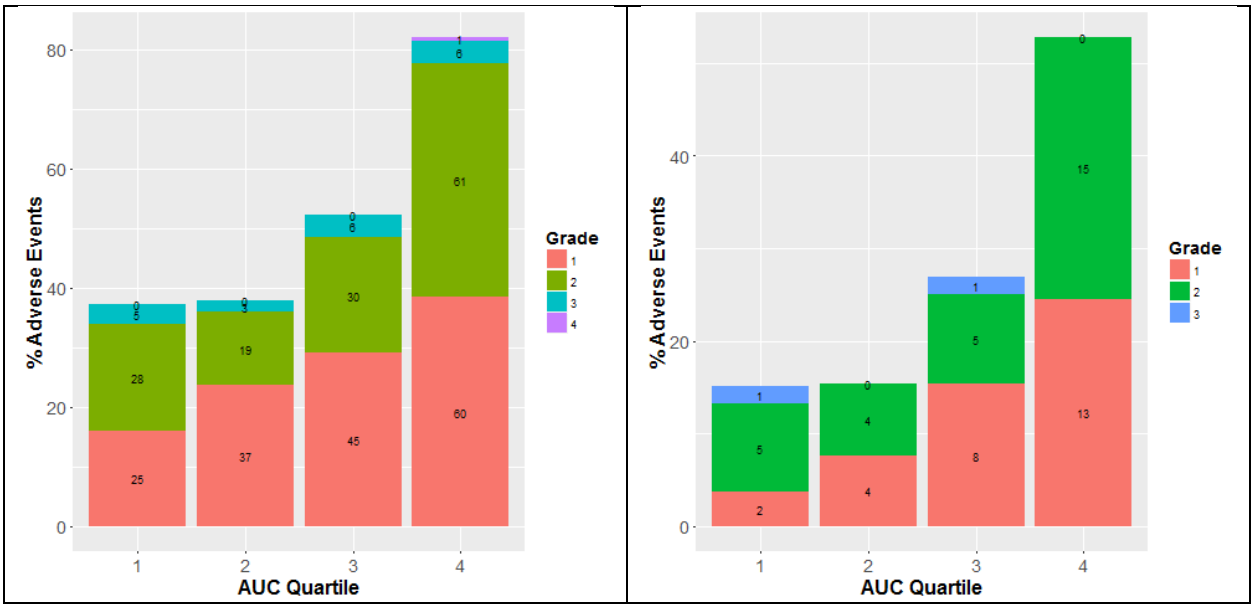
(Source: FDA Analysis)

Figure 18: Exposure-Response Relationship for Vomiting



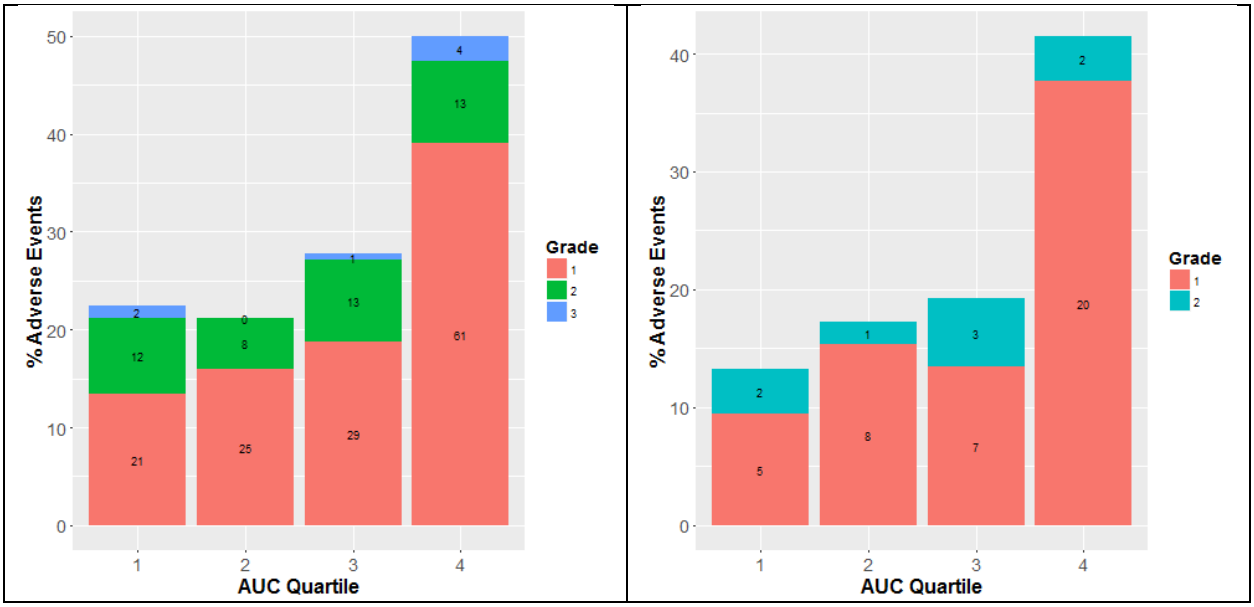
(Source: FDA Analysis)

Figure 19: Exposure-Response Relationship for Decreased Appetite



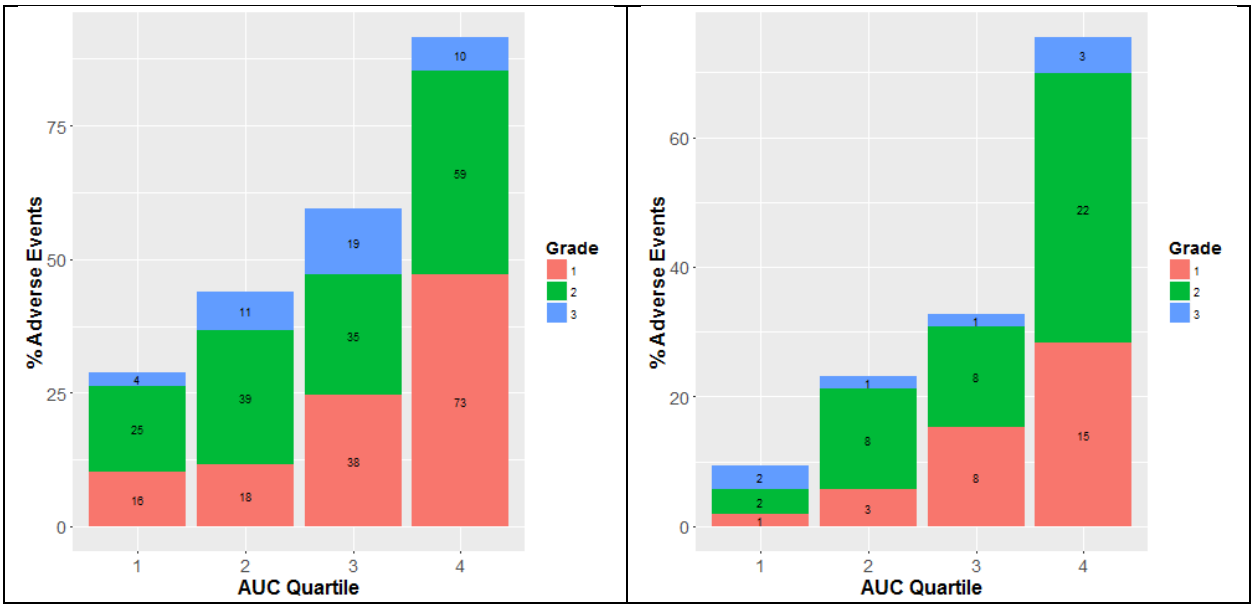
(Source: FDA Analysis)

Figure 20: Exposure-Response Relationship for Decreased Weight



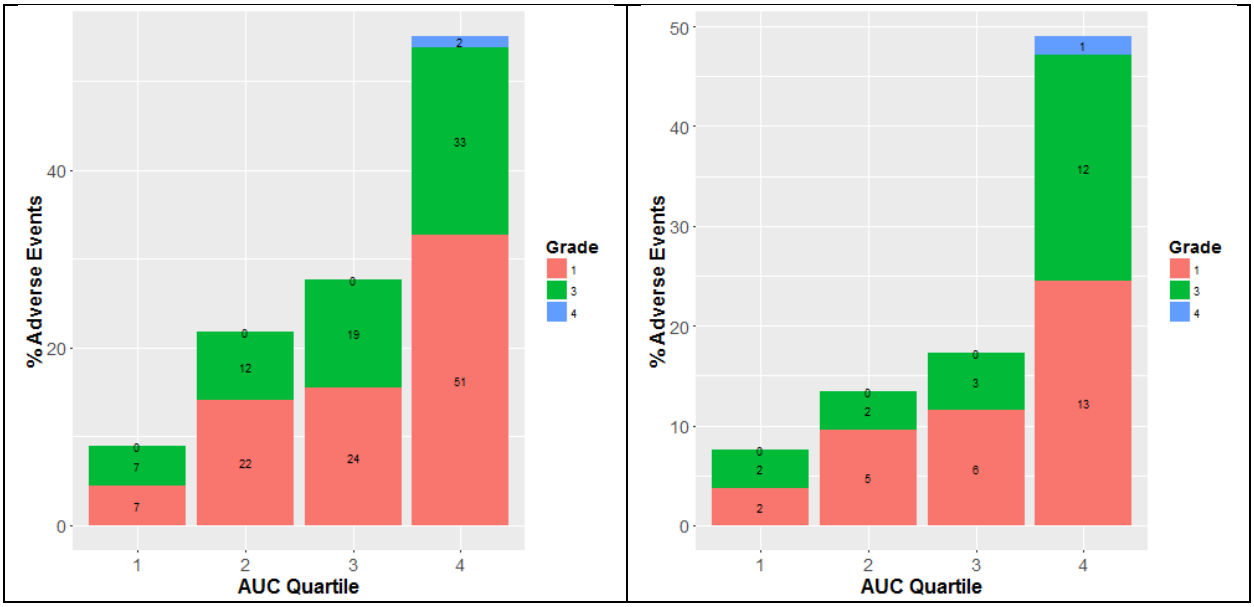
(Source: FDA Analysis)

Figure 21: Exposure-Response Relationship for Fatigue



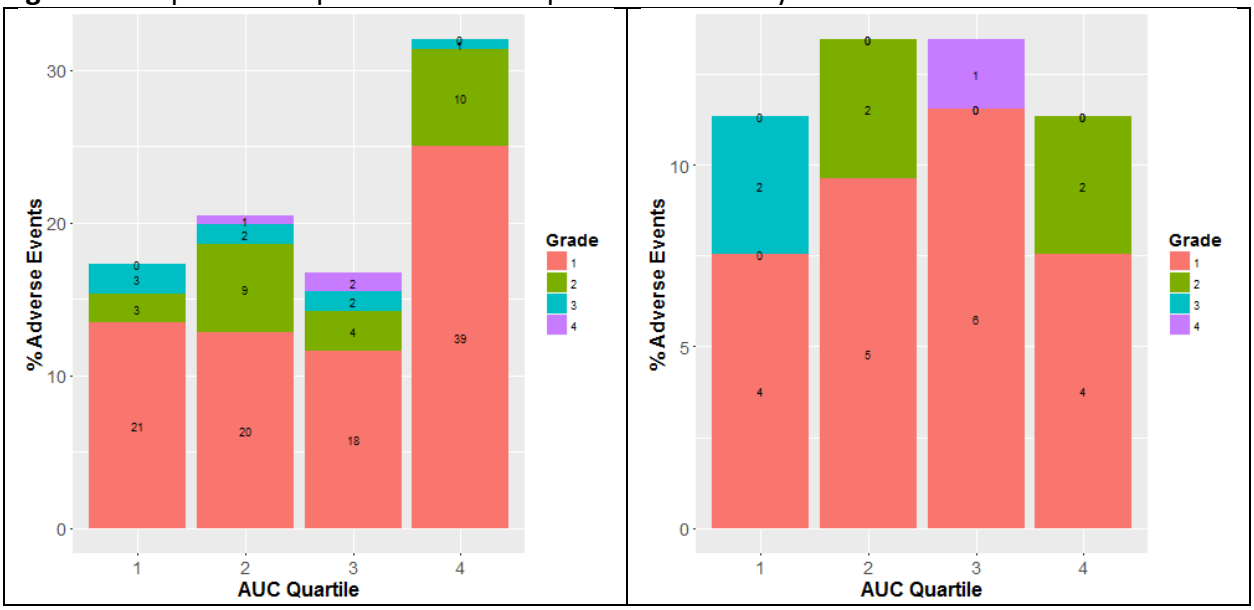
(Source: FDA Analysis)

Figure 22: Exposure-Response Relationship for Hyponatremia



(Source: FDA Analysis)

Figure 23: Exposure-Response Relationship for Ocular Safety Events

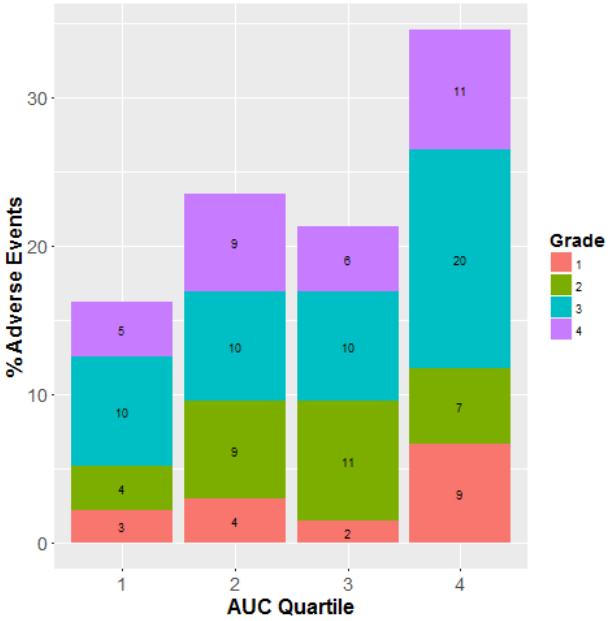


(Source: FDA Analysis)

A sensitivity analysis was performed, excluding study KCP-330-012 (STORM) from the full PK-safety analysis set to investigate whether the advanced disease state of patients in this study was influencing the trend for exposure-response. The results are shown in Figure 24 to Figure 33. Removing study KCP-330-012 did not appear to affect the nature of the exposure-response relationship for each adverse event. For each of the following graphs (Figure 24 to Figure 33),

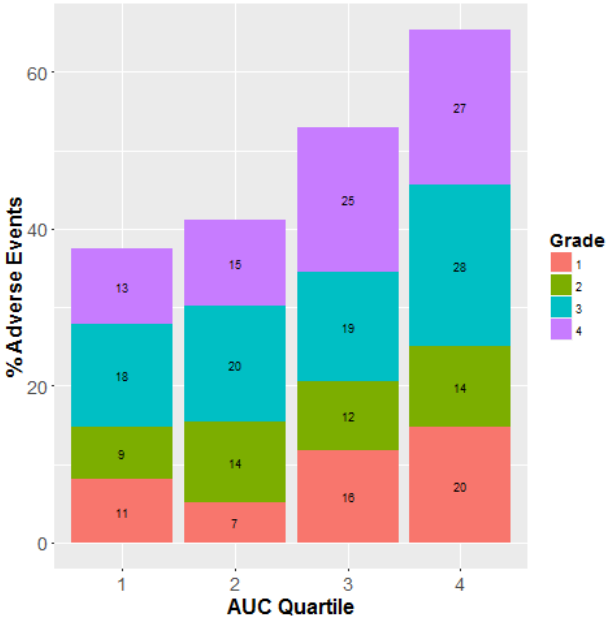
the y-axis is the percentage of subjects with the adverse event. The numbers in the plot indicate the number of individuals with that grade event in each AUC quartile. The grade of the adverse event refers to the grade at the first occurrence for that individual.

Figure 24: Exposure-Response Relationship for Neutropenia and Decreased Neutrophil Count



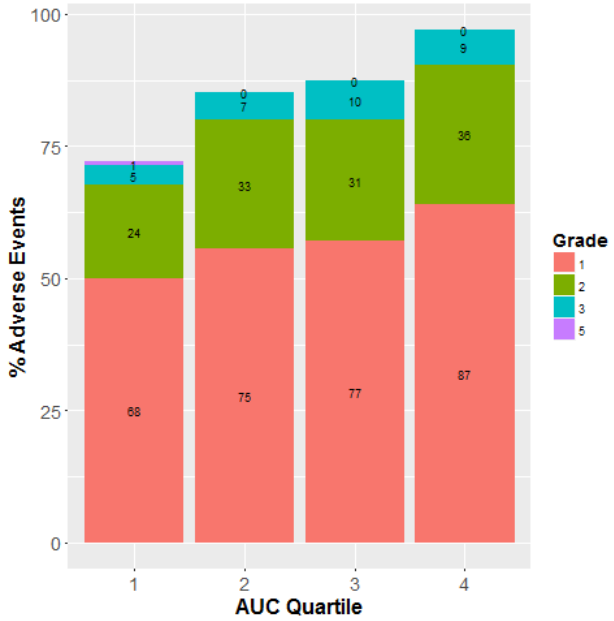
Full PK-Safety dataset minus STORM data
(Source: FDA Analysis)

Figure 25: Exposure-Response Relationship for Thrombocytopenia



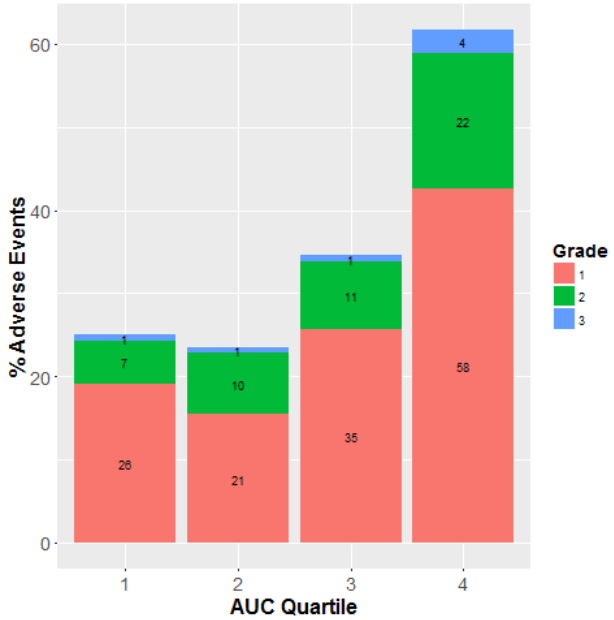
Full PK-Safety dataset minus STORM data
(Source: FDA Analysis)

Figure 26: Exposure-Response Relationship for Gastrointestinal Disorders



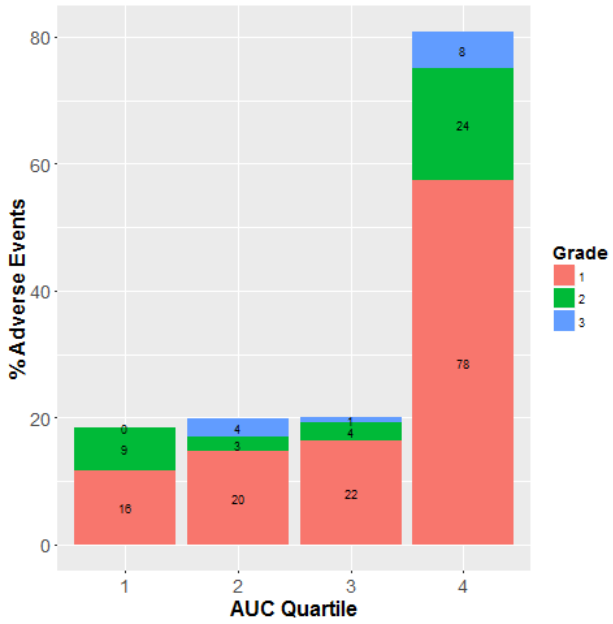
Full PK-Safety dataset minus STORM data
(Source: FDA Analysis)

Figure 27: Exposure-Response Relationship for Diarrhea



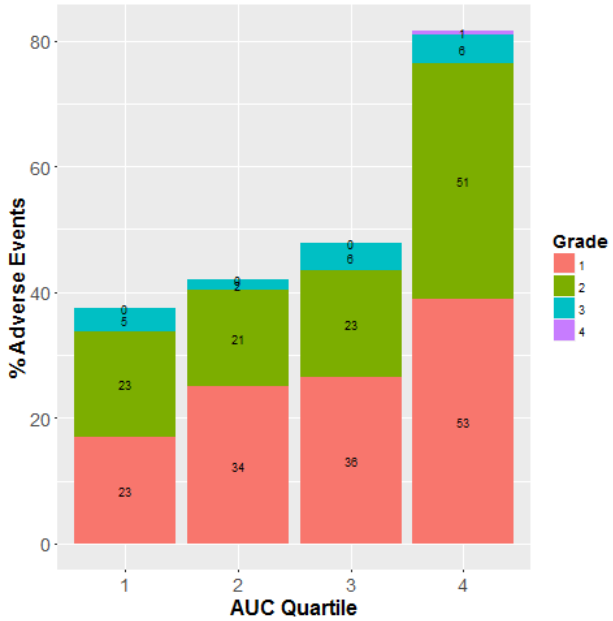
Full PK-Safety dataset minus STORM data
(Source: FDA Analysis)

Figure 28: Exposure-Response Relationship for Vomiting



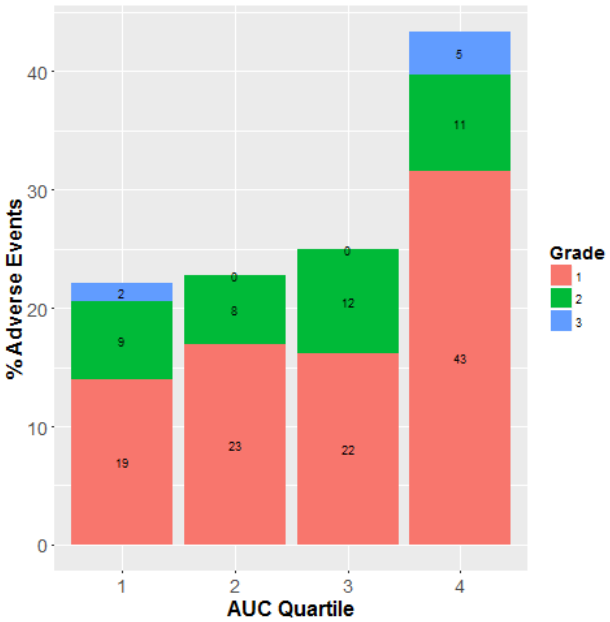
Full PK-Safety dataset minus STORM data
(Source: FDA Analysis)

Figure 29: Exposure-Response Relationship for Decreased Appetite



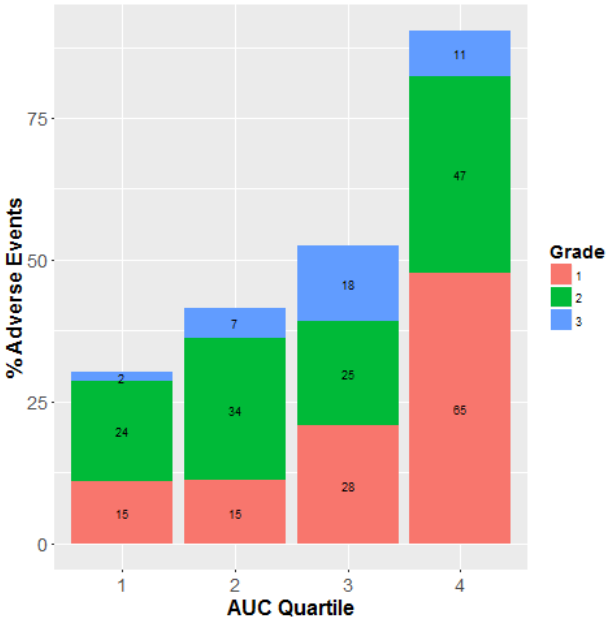
Full PK-Safety dataset minus STORM data
(Source: FDA Analysis)

Figure 30: Exposure-Response Relationship for Decreased Weight



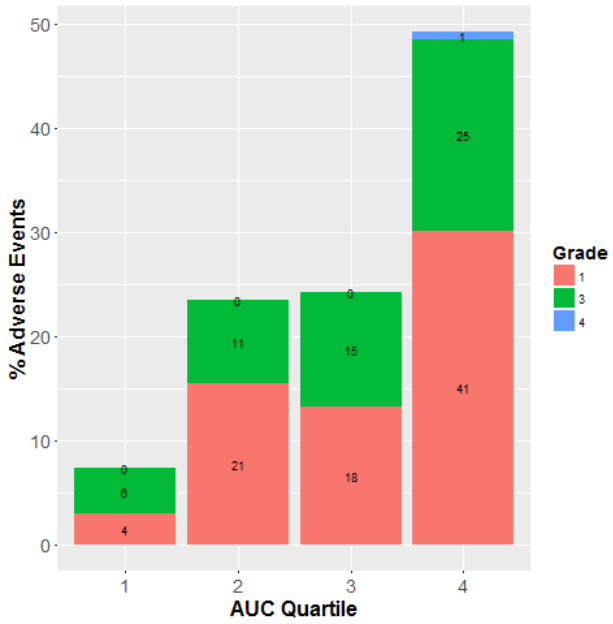
Full PK-Safety dataset minus STORM data
(Source: FDA Analysis)

Figure 31: Exposure-Response Relationship for Fatigue



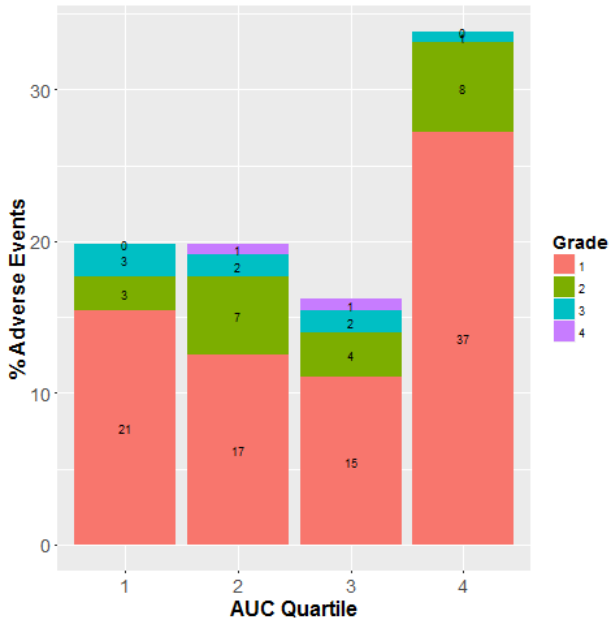
Full PK-Safety dataset minus STORM data
(Source: FDA Analysis)

Figure 32: Exposure-Response Relationship for Hyponatremia



Full PK-Safety dataset minus STORM data
(Source: FDA Analysis)

Figure 33: Exposure-Response Relationship for Ocular Safety Events



Full PK-Safety dataset minus STORM data
(Source: FDA Analysis)

In addition, the correlation between the AUC quartile and potentially relevant patient risk factors were evaluated and summarized in Table 67 and Table 68. While most of the baseline

risk factors appear to be reasonably balanced across AUC quartiles, it is possible that correlations of selinexor exposure with ECOG score and percentage of patients with at least 4 prior therapies may have contributed to the E-R relationships observed with some adverse events.

Table 67: Baseline Patient Characteristics by Time-averaged AUC Quartile for Each Adverse Event

	AUCQ	N	Platelet (10^9/L)	Neutrophil (1000/mL)	Sodium (mmol/L)	Age (yrs)	ECOG (mean)	≥ 4 Prior Therapies (%)	Duration Since Initial Diagnosis (days)
Hypo-natremia	1	156	130	2.92	**140**	68.2	0.67	15.4	1107
	2	156	137	3.11	**139**	67.6	0.73	18.6	968
	3	155	145	4.41	**138**	66.9	0.87	20.0	818
	4	156	125	3.51	**137**	67.7	1.08	31.4	1080
Neutro-penia	1	156	129	**3.16**	139	68.0	0.74	19.2	1166
	2	156	133	**3.04**	139	67.6	0.67	19.9	948
	3	155	140	**4.26**	138	67.0	0.94	25.2	901
	4	156	134	**3.49**	138	67.7	1.02	21.2	978
Thrombo-cytopenia	1	156	**138**	2.90	139	66.9	0.69	10.9	970
	2	156	**147**	3.03	139	67.5	0.78	23.1	989
	3	155	**132**	4.30	138	67.2	0.85	27.1	938
	4	156	**122**	3.61	138	68.5	1.03	24.4	1058
Decreased Appetite	1	156	130	2.94	140	66.5	0.69	13.5	1126
	2	156	136	3.03	138	68.7	0.72	19.2	1012
	3	155	136	3.52	139	66.8	0.91	23.9	1033
	4	156	135	4.26	138	67.9	1.01	28.8	843
Diarrhoea	1	156	118	2.83	139	67.9	0.69	17.9	1122
	2	156	140	2.90	139	69.4	0.66	14.7	890
	3	155	145	4.57	139	65.4	0.93	23.9	974
	4	156	131	3.54	138	67.8	1.06	28.8	998
Eye Disorders	1	156	125	2.93	139	68.9	0.74	18.6	1130
	2	156	134	2.96	139	67.7	0.70	21.8	1066
	3	155	137	4.36	138	67.7	0.92	24.5	962
	4	156	140	3.68	138	66.0	1.03	20.5	822
Fatigue	1	156	126	2.77	140	68.1	0.76	13.5	1161
	2	155	128	3.13	138	68.3	0.75	18.1	875
	3	155	135	3.63	138	67.2	0.89	21.9	1026
	4	155	145	4.22	138	66.9	0.96	31.6	951
GI Disorders	1	156	119	2.65	138	69.3	0.73	14.1	993
	2	155	144	3.37	139	69.3	0.76	13.5	907
	3	155	134	3.25	138	67.0	0.84	25.2	866
	4	155	135	4.33	138	65.9	0.98	32.9	1160
Decreased Weight	1	156	131	3.12	139	68.1	0.68	14.7	1081
	2	156	133	3.23	139	67.8	0.74	19.2	975
	3	155	125	3.16	138	67.0	0.93	22.6	858
	4	156	146	4.44	138	67.5	1.02	28.8	1056
Vomiting	1	156	122	2.61	139	68.9	0.68	16.0	1058
	2	155	127	3.04	138	68.3	0.70	16.8	998
	3	155	141	4.09	139	67.3	0.90	21.9	981
	4	156	144	4.06	138	66.2	1.05	30.1	943

Full PK-Safety dataset
(Source: FDA Analysis)

Table 68: Baseline Patient Characteristics by Time-averaged AUC Quartile for Each Adverse Event (Sensitivity Analysis Dataset)

	AUCQ	N	Platelet (10^9/L)	Neutrophil (1000/mL)	Sodium (mmol/L)	Age (yrs)	ECOG (mean)	≥ 4 Prior Therapies (%)	Duration Since Initial Diagnosis (days)
Hypo-natremia	1	136	126	2.74	**140**	68.8	0.64	9.6	847
	2	136	128	2.99	**139**	68.8	0.67	8.8	840
	3	136	140	4.59	**138**	68.0	0.87	10.3	624
	4	136	126	3.98	**138**	68.7	1.13	13.2	592
Neutro-penia	1	136	125	**3.05**	139	68.6	0.66	9.6	863
	2	136	123	**3.20**	139	69.4	0.68	9.6	733
	3	136	136	**4.59**	138	67.5	0.91	13.2	619
	4	136	135	**3.51**	138	68.7	1.06	9.6	688
Thrombo-cytopenia	1	136	**136**	2.80	140	67.2	0.65	5.9	756
	2	136	**129**	2.97	139	69.9	0.76	12.5	771
	3	136	**131**	4.70	138	67.7	0.82	10.3	651
	4	136	**125**	3.76	138	69.1	1.06	13.2	706
Decreased Appetite	1	136	126	2.76	140	67.1	0.65	8.1	740
	2	136	121	3.05	138	70.2	0.72	8.1	800
	3	136	141	3.70	139	67.2	0.87	9.6	742
	4	136	130	4.55	138	69.2	1.03	16.2	614
Diarrhoea	1	136	119	2.65	140	68.7	0.67	10.3	820
	2	136	126	2.90	138	70.5	0.60	8.1	746
	3	136	147	5.06	139	66.0	0.89	8.1	664
	4	136	126	3.59	138	69.0	1.12	15.4	668
Eye Disorders	1	136	124	2.63	140	69.4	0.66	11.0	779
	2	136	127	3.28	139	69.0	0.71	9.6	786
	3	136	128	4.66	138	69.5	0.87	9.6	666
	4	136	140	3.73	138	66.5	1.07	11.8	651
Fatigue	1	136	126	2.94	140	68.1	0.72	8.1	791
	2	136	114	2.98	138	70.2	0.71	11.1	699
	3	136	134	3.62	138	67.4	0.87	6.7	710
	4	136	143	4.58	138	68.4	0.98	15.4	697
GI Disorders	1	136	117	2.46	139	70.1	0.68	6.6	797
	2	136	134	3.33	139	69.6	0.73	6.7	713
	3	136	140	3.57	138	68.8	0.82	11.1	674
	4	136	126	4.46	138	67.1	0.99	17.6	714
Decreased Weight	1	136	130	3.02	140	68.8	0.65	8.8	838
	2	136	129	3.17	139	68.7	0.71	11.0	754
	3	136	120	3.50	138	68.7	0.92	10.3	647
	4	136	141	4.65	138	68.0	1.03	11.8	656
Vommiting	1	136	124	2.52	139	69.5	0.64	8.8	802
	2	136	121	3.27	138	69.6	0.70	9.6	766
	3	136	140	4.35	139	67.5	0.85	7.4	681
	4	136	134	4.10	138	67.9	1.08	15.4	646

Full PK-Safety dataset minus STORM data
(Source: FDA Analysis)

13.3.4 Population PK Analysis

The applicant conducted a population PK analyses to describe the pharmacokinetics of selinexor and facilitate AUC estimates for their exposure response analysis. PK data from studies KCP-330-001, KCP-330-002, KCP-330-003, KCP-330-008, KCP-330-009, KCP-330-010, and KCP-330-012 were used in the analysis. Patient demographics are outlined in Table 69 and Table 70 and PK data by study and sampling schedule are described in Table 71.

Table 69: Summary of Baseline Demographic Characteristics for the PK Overall Database

Statistic	Mean	SD	Median	Min	Max	n
Age (yr)	65.4	12.3	68	18	94	720
Weight (kg)	77.1	18.4	75	36.5	169	720
BMI (kg/m^2)	26.7	5.42	25.8	10.6	51.4	720
BSA (m^2)	1.88	0.244	1.87	1.05	2.82	720
Albumin (g/L)	37.3	5.66	38	4.6	65	720
Alkaline Phosphotase (IU/L)	103	74.7	82.2	26.1	780	720
Aspartate Transaminase (IU/L)	27.9	18.7	23	3.01	169	720
Alanine transferase (IU/L)	26.5	22.9	20	3.01	268	720
Bilirubin (mg/dL)	0.572	0.448	0.5	0.1	6	720
Creatinine Clearance (mL/min)	85.2	36.5	78	20	338	720

(Source: Applicant's Population PK Report, Table 5)

Table 70: Summary of Categorical Demographic Characteristics for the PK Overall Database

Number	Covariate	Number	Covariate
131	KCP-330-001	422	Male
60	KCP-330-002	298	Female
37	KCP-330-003	17	Unknown
195	KCP-330-008	607	White
192	KCP-330-009	46	Black
26	KCP-330-010	15	Asian
79	KCP-330-012	35	Other
623	Hematologic	261	Normal Renal Function
97	Solid Tumor	277	Mild Renal Impariment
188	Capsule	167	Moderate Renal Impairment
526	Tablet	15	Severe Renal Impairment
5	Suspension	611	Normal Hepatic Function
1	Capsule/Suspension	100	Mild Hepatic Impariment
		6	Moderate Hepatic Impairment
		3	Severe Hepatic Impairment

(Source: Applicant's Population PK Report, Table 6)

Table 71: Summary of Clinical Studies Used in the Population PK Analysis

Study [Reference]	Study Population	Study Design	Study Drug Dosage Regimens	# of Subjects with PK	Average Number of PK/ Patient
Study KCP-330-001 [2]	Adult Cancer patients	A Phase I Study of the Safety, Pharmacokinetics and Pharmacodynamics of Escalating Doses of the Selective Inhibitor of Nuclear Export/SINE Compound KPT-330 in Patients with Advanced Hematological Malignancies	3-80 mg/m^2	131	15.1
Study KCP-330-002 [3]	Adult Cancer patients	A Phase I Study of the Safety, Pharmacokinetics and Pharmacodynamics of Escalating Doses of the Selective Inhibitor of Nuclear Export/SINE Compound KPT 330 in Patients with Advanced or Metastatic Solid Tumor Malignancies	3 - 85 mg/m^2	112	15.7
Study KCP-330-003 [4]	Adult Cancer patients	An Open-Label Phase 1B Trial to Evaluate the Effects of Food and Formulation on Pharmacokinetics of the Oral Selective Inhibitor of Nuclear Export/SINE Compound KPT-330 in Patients with Soft-Tissue or Bone Sarcoma	30 mg/m^2 60 mg	37	42.5
Study KCP-330-008 [5]	Adult Cancer patients	SOPRA (Selinexor in Older Patients with Relapsed AML): A Randomized, Open Label, Phase 2 Study of the Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330) versus Specified Physician's Choice in Patients ≥ 60 Years Old with Relapsed/Refractory Acute Myeloid Leukemia (AML) Who are Ineligible for Intensive Chemotherapy and/or Transplantation	55 mg/m^2 60 mg twice weekly	207	13.4
Study KCP-330-009 [6]	Adult Cancer patients	ADAL: Selinexor Against Diffuse Aggressive Lymphoma: A Phase 2b Open-label Study of Selinexor (KPT-330) in Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma (DLBCL)	60 mg days 1 and 3 of each week Or 100 mg day 1 of each week	194	9.8
Study KCP-330-010 [7]	Adult Cancer patients	SIRRT Study: Selinexor in Initial or Relapsed/Refractory Richter's Transformation A Phase 2 Study of the Safety and Anti-tumor Activity of the Oral Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330) in Patients with Initial or Refractory / Relapsed Richter's Transformation (RT)	60 mg twice weekly during Weeks 1-4 of each 4-week cycle	26	9.1
Study KCP-330-012 [8]	Adult Cancer patients	STORM (Selinexor Treatment of Refractory Myeloma)A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) Plus Low Dose Dexamethasone (Sd) in Patients with Multiple Myeloma Previously Treated with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib, and Daratumumab, and Refractory to Prior Treatment with Glucocorticoids, an Immunomodulatory Agent, a Proteasome Inhibitor, and the anti-CD38 mAb	80 mg plus low-dose dexamethasone (20 mg) (S+D) twice weekly	79	10.1

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

(Source: Applicant's Population PK Report, Table 1)

The Applicant's final population PK model of selinexor is a 1-compartment linear model with first-order absorption following a lag time and first order elimination. After evaluation of the covariates it was determined that sex and BMI were covariates on CL/F, and BSA and ALB were covariates on V/F and age is a covariate on both Ka and Lag. The parameters for the final model are presented in Table 72. Shrinkage is reported for the final model in Table 73. Goodness of fit plots and the visual predictive check are shown in Figure 34 and Figure 35.

Table 72: Final Population PK Model Parameters

Parameter (Units)	Model Parameter	Estimate	Standard Error (%CV)	Bootstrap Lower 95% CI	Bootstrap Median	Bootstrap Upper 95% CI
CL/F	θ1	17.7	2	17.40	17.65	18.40
CL/F for moderate and severe HI	θ7	15.2	11.6	13.10	14.95	19.51
V/F	θ2	125	1.9	123.00	125.00	132.00
Ka	θ3	1.03	7.1	0.98	1.03	1.20
Lag	θ4	0.331	3.9	0.31	0.32	0.36
Residual Error	θ5	73.7	1	72.50	73.60	77.11
Shared eta parameter	θ6	0.206	48.2	-0.02	0.19	0.61
Effect of Sex on CL	θ8	-0.191	11	-0.20	-0.18	-0.14
Effect of BMI on CL	θ13	0.447	15.5	0.39	0.45	0.61
Effect of BSA on V	θ15	1.3	8.8	1.18	1.27	1.57
Effect of ALB on V	θ16	-0.222	39.7	-0.30	-0.23	-0.04
Effect of Age on Ka	θ17	0.709	31.2	0.50	0.71	1.33
Effect of Age on Lag	θ18	0.487	0.1	0.10	0.34	1.07
IIV CL/F (%CV)	η1	15.7	4.8	13.80	15.20	21.22
IIV Ka (%CV)	η2	124.9	4.5	120.10	124.90	139.60
IIV Lag (%CV)	η4	39.9	6.9	39.00	42.20	52.31
Corr(CL/F, Ka)	--	-0.447	NE	-0.62	-0.50	-0.18

CI –confidence interval, CL/F – apparent from central compartment, CV – coefficient of variation, V/F – apparent central volume of distribution, Ka – absorption rate constant, Lag – lag time, IIV – interindividual variability, PPK – population pharmacokinetics, NE- not estimated, BMI – body mass index, BSA –body surface area, ALB – albumin, HI – hepatic impairment

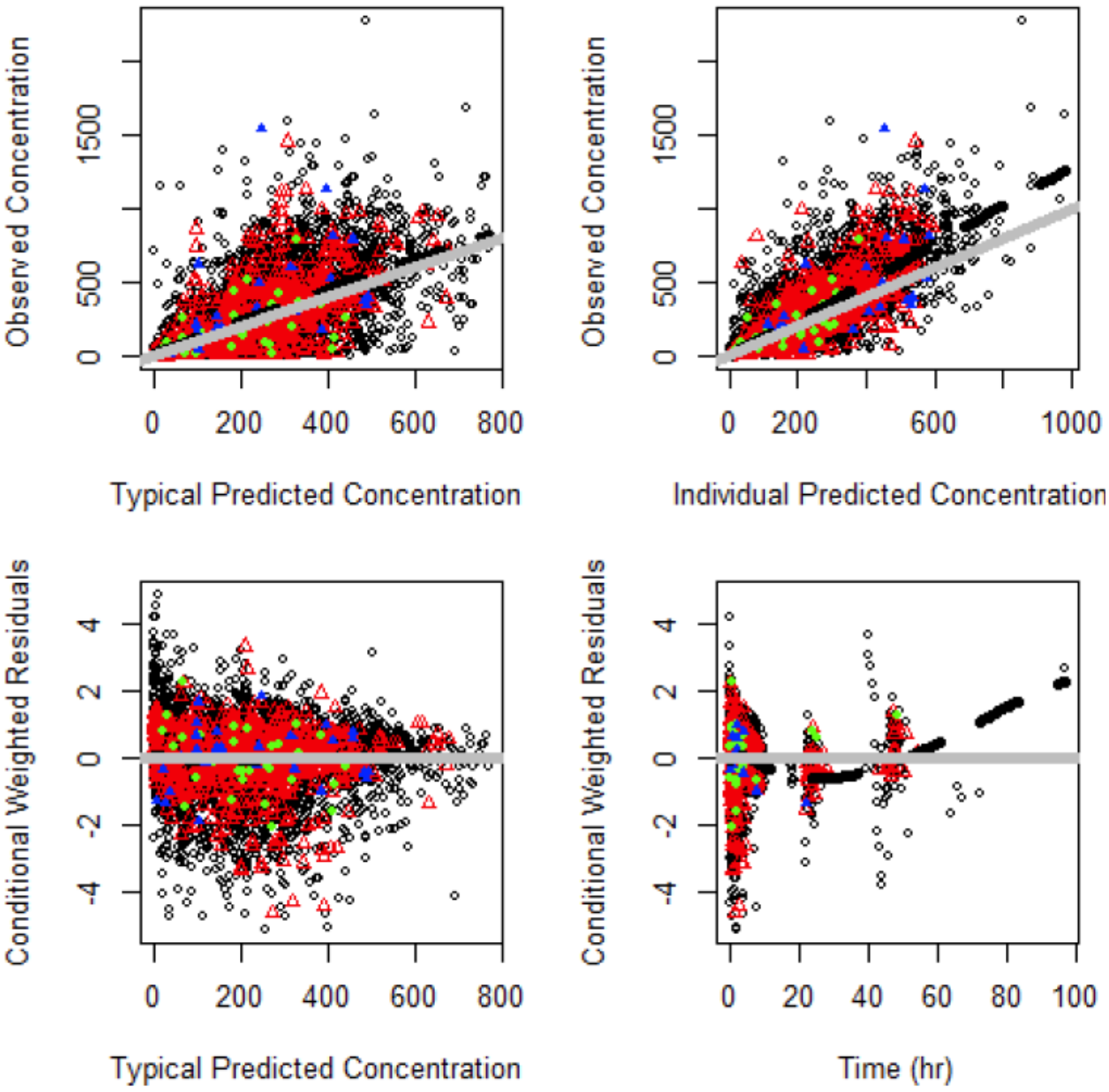
(Source: Applicant's Population PK Report, Table 24)

Table 73: Performance Metrics of the Final Population PK Model

Statistic	IIV CL	IIV Ka	IIV Lag
ETAPval	0.339	0.849	0.762
ETAshr%	40.7	16.9	52.3
EBVshr%	46.2	16.6	53.3
EPSshr%	4.2	Condition Number	3.54

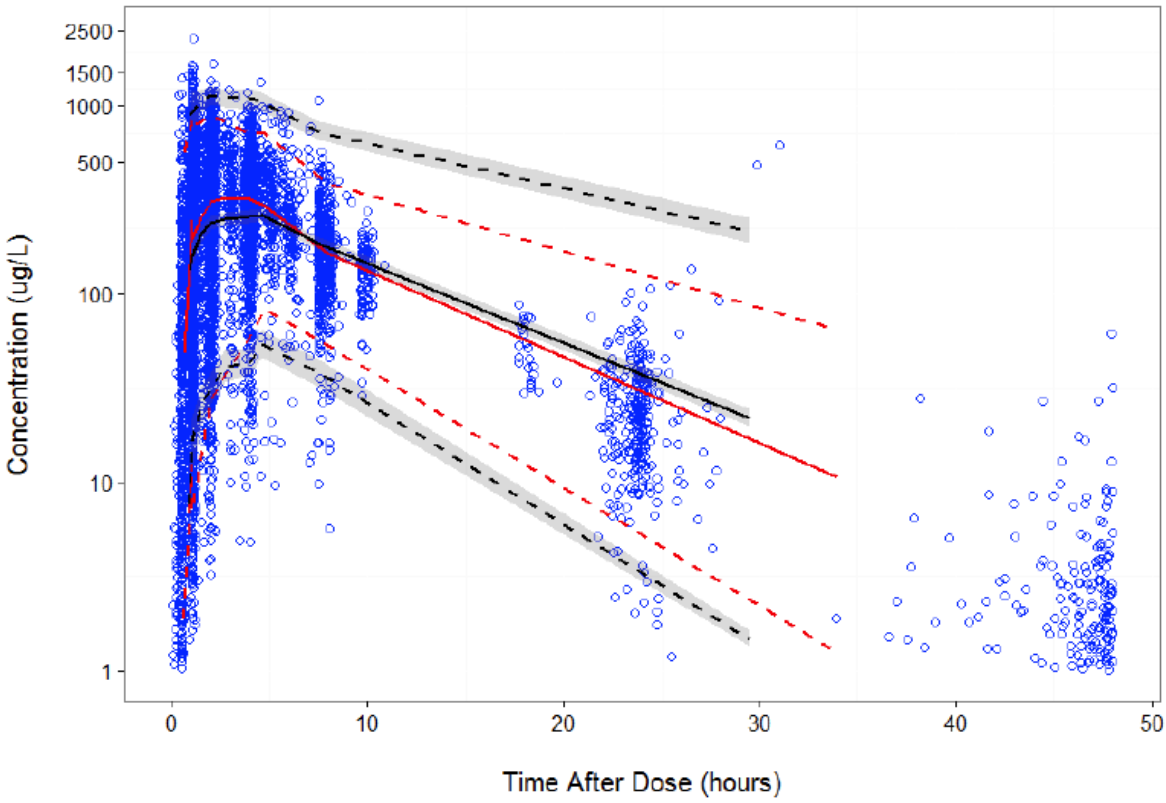
(Source: Applicant's Population PK Report, Table 25)

Figure 34: Goodness of Fit Plots for the Final Population PK Model



(Source: Applicant's Population PK Report, Figure 19)

Figure 35: Visual Predictive Check for the Final Population PK Model



(Source: Applicant's Population PK Report, Figure 26)

Reviewer's Comments: *The Applicant's population PK analysis is acceptable to label the pharmacokinetics characteristics of selinexor and obtain post hoc PK estimates for the exposure-response analysis. The model is limited with regards to evaluation of drug-drug interaction potential. While drug-drug interaction data were available, the high degree of shrinkage in the eta residual for CL means that further quantitative covariate evaluation is challenging as the model is already approaching an overparameterized state. Conclusions regarding additional covariates may not be meaningful.*

13.4 Clinical Appendices

Preferred Term Grouping

The following grouping of preferred terms was utilized for analyses in section 7.4.5.

<u>Blood and lymphatic system disorders</u>
Anemia = anemia and hematocrit decreased
Neutropenia = neutropenia and neutrophil count decreased
Thrombocytopenia = thrombocytopenia and platelet count decreased

Cardiac disorders
Cardiac failure = cardiac failure and cardiac failure congestive
Tachycardia = tachycardia and sinus tachycardia

Gastrointestinal disorders
Abdominal pain = abdominal pain, abdominal pain upper, and abdominal pain lower

General disorders and administration site conditions
Fatigue = fatigue and asthenia

Infections and infestations
Bacteremia = bacteremia, Escherichia bacteremia, Staphylococcal bacteremia, and Streptococcal bacteremia
Influenza = influenza and H1N1 influenza
Pneumonia = pneumonia, atypical pneumonia, lung infection, lower respiratory tract infection, pneumocystis jirovecii pneumonia, pneumonia aspiration, pneumonia influenzal, and pneumonia viral
Sepsis = sepsis, fungal sepsis, staphylococcal sepsis, and septic shock
Upper respiratory tract infection = upper respiratory tract infection, respiratory tract infection, pharyngitis, nasopharyngitis, bronchitis, bronchiolitis, respiratory syncytial virus infection, parainfluenza virus infection, rhinitis, rhinovirus infection, and adenovirus infection

Injury, poisoning, and procedural complications
Fracture = pathologic fracture, cervical vertebral fracture, clavicle fracture, compression fracture, femur fracture, hip fracture, humerus fracture, lower limb fracture, rib fracture, sternal fracture, lower limb fracture, and upper limb fracture

Metabolism and nutrition disorders
Hypercreatininemia = hypercreatininemia and hypercreatinemia

Psychiatric disorders
Mental status changes = mental status changes, confusional state, and delirium

Nervous system disorders
Neuropathy = neuropathy peripheral, peripheral sensory neuropathy, and polyneuropathy

Renal and urinary disorders
Acute kidney injury = acute kidney injury and renal injury

Respiratory, thoracic, and mediastinal disorders
Respiratory failure = respiratory failure, acute respiratory failure, and respiratory arrest

Cough = cough, productive cough, and upper-airway cough syndrome
Dyspnea = dyspnea, dyspnea exertional, and dyspnea at rest

13.5 Statistical Appendices

RWD Information Request History

Table 74: RWD Information Request History

Date	Document Type	Details
8/6/2018	NDA Submission	KS-50039 Study Report
12/12/2018	FDA IR	• No pre-specified protocol or SAP • Patients in FHAD arm should be receiving active anti-myeloma therapies • Definition of index date • High % ECOG status missing
12/16/2018	Applicant's Response to IR	• Acknowledge the need to discuss protocols with FDA in advance in the future • Applicant acknowledges it may cause confusion to present FHAD and STORM KM curves in the same graph • Real world analysis results were meant only to show agreement with results in the literature
12/27/2018	Applicant's Response to IR	• Anti-myeloma regimens used after index date (end date of 1st regimen patients became penta-exposed) • New proposed index date definition: start date of 1st therapy patients became penta-exposed and triple-class-refractory (many patients had other therapies between the index date and start date of selinexor in STORM)
1/4/2019	FDA IR	• FHAD: the index date should be the start date of 1st regimen received after the patient became penta-exposed and triple-class refractory, and patients that did not receive subsequent anti-myeloma therapy should be excluded • STORM: the index date should be the start date of selinexor received after the patient became penta-exposed and triple-class refractory; include only patients who received selinexor after meeting criteria for penta-exposed and triple-class-refractory
1/11/2019	Applicant's Response to IR	Submitted more sensitivity analyses with adjustment of confounding factors one by one

(Source: FDA)

STORM Study Phase 2b Inclusion/Exclusion Criteria

The following are the Inclusion/Exclusion Criteria from Amendment 3, Protocol Version 4.0, which expanded enrollment to include an additional ~130 patients, revised the protocol to make Part 2 the ITT population for the primary efficacy analysis, and revised the patient population to evaluate patients with more refractory disease.

Inclusion Criteria:

Patients must meet all of the following inclusion criteria to be eligible to enroll in this study:

1. Written informed consent in accordance with federal, local, and institutional guidelines.
2. Age ≥18 years at the time of signing informed consent.
3. Measurable MM based on modified IMWG guidelines as defined by at least one of the following:
   a. Serum M-protein ≥ 0.5 g/dL by serum electrophoresis (SPEP) or, for IgA myeloma, by quantitative IgA
   b. Urinary M-protein excretion ≥200 mg/24 hours
   c. FLC ≥ 100 mg/L, provided that the FLC ratio is abnormal
   d. If serum protein electrophoresis is felt to be unreliable for routine M-protein measurement, then quantitative Ig levels by nephelometry or turbidometry are acceptable
4. Patients must have previously received ≥3 anti-MM regimens including: an alkylating agent, lenalidomide, pomalidomide, bortezomib, carfilzomib, either daratumumab or isatuximab, and a glucoorticoid. There is no upper limit on the number of prior therapies provided that all other inclusion/exclusion criteria are met.
5. MM refractory to previous treatment with one or more glucocorticoids, parenteral PI (i.e., bortezomib and/or carfilzomib), IMiD (i.e., lenalidomide and/or pomalidomide), and anti-CD38 mAb (i.e., either daratumumab or isatuximab). Refractory is defined as ≤ 25% response to therapy, or progression during therapy or progression within 60 days after completion of therapy.
6. Multiple myeloma that is refractory to the patient's most recent anti-MM regimen. (Documented severe intolerance to the patient's last therapy is allowed upon approval by the Medical Monitor).
7. Any clinically significant non-hematological toxicities (except for peripheral neuropathy as described in exclusion criterion #18) that patients experienced from treatments in previous clinical studies must have resolved to ≤ Grade 2 by Cycle 1 Day 1.
8. Adequate hepatic function within 21 days prior to Cycle 1 Day 1: total bilirubin < 2x upper limit of normal (ULN) (except patients with Gilbert's syndrome who must have a total bilirubin of < 3x ULN), AST < 2.5x ULN and ALT < 2.5x ULN.
9. Adequate renal function within 21 days prior to Cycle 1 Day 1: estimated creatinine clearance of ≥ 20 mL/min, calculated using the formula of Cockcroft and Gault.
10. Female patients of child-bearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at screening. Male

patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose of study treatment.

11. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2.
12. Adequate hematopoietic function within 21 days prior to Cycle 1 Day 1 (See Exclusion Criterion #21 for transfusion washout periods for RBCs and platelets):
    a. Total WBC count ≥ 1,500/mm^3
    b. ANC ≥ 1000/mm^3
    c. 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. [Platelet transfusions < 1 week prior to Cycle 1 Day 1 are prohibited (see below).]
13. Hemoglobin level ≥ 8.5 gm/dL on Cycle 1 Day 1. In certain cases, patients with stable baseline hemoglobin level > 8.0 may be included following approval by the Medical Monitor. [Red blood cell transfusions < 2 weeks prior to Cycle 1 Day 1 are prohibited (see below).]
14. Confirmation of patient eligibility for study participation with the Medical Monitor.

Exclusion Criteria:

1. Active smoldering MM.
2. Active plasma cell leukemia.
3. Documented systemic amyloid light chain amyloidosis.
4. Active central nervous system (CNS) MM.
5. Pregnancy or breastfeeding.
6. Radiation, chemotherapy, or immunotherapy or any other anticancer therapy ≤ 2 weeks prior to Cycle 1 Day 1, and radio-immunotherapy 6 weeks prior to Cycle 1 Day 1.
7. Active graft vs. host disease (after allogeneic stem cell transplantation) at Cycle 1 Day 1.
8. Life expectancy of < 4 months.
9. Major surgery within four weeks prior to Cycle 1 Day 1.
10. Active, unstable cardiovascular function:
    a. Symptomatic ischemia, or
    b. Uncontrolled clinically-significant conduction abnormalities (e.g., patients with ventricular tachycardia on antiarrhythmics are excluded; patients with 1st degree atrioventricular (AV) block or asymptomatic left anterior fascicular block/right bundle branch block (LAFB/RBBB) will not be excluded), or
    c. Congestive heart failure (CHF) of New York Heart Association (NYHA) Class ≥ 3, or
    d. Myocardial infarction (MI) within 3 months prior to Cycle 1 Day 1.
11. Active, uncontrolled hypertension.

12. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to first dose.
13. Known HIV seropositive.
14. Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface antigen).
15. Prior malignancy that required treatment or has shown evidence of recurrence (except for non-melanoma skin cancer or adequately treated cervical carcinoma in situ) during the 5 years prior to enrollment. Cancer treated with curative intent > 5 years previously and without evidence of recurrence will be allowed.
16. Active GI dysfunction interfering with the ability to swallow tablets, or any GI dysfunction that could interfere with absorption of study treatment.
17. Grade ≥ 3 peripheral neuropathy, and Grade 2 panful neuropathy, within 21 days prior to Cycle 1 Day 1.
18. Serious, active psychiatric or medical conditions which, in the opinion of the Investigator, could interfere with treatment.
19. Participation in an investigational anti-cancer study within 21 days prior to Cycle 1 Day 1.
20. Receipt of transfusions as follows:
    a. Platelet infusion within 1 week prior to Cycle 1 Day 1.
    b. RBC transfusion within 2 weeks prior to Cycle 1 Day 1.
21. Known intolerance to glucocorticoid therapy at Cycle 1 Day 1.
22. Unable or Unwilling to comply with protocol requirements, including providing a 24-hour urine sample at the required study time points.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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HAO ZHU on behalf of LIAN MA
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I concur.

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