FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting
February 26, 2019

NDA 212306
Selinexor
Applicant: Karyopharm Therapeutics, Inc.

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Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
APL	Acute promyelocytic leukemia
Ara-C	Cytarabine
AST	Aspartate aminotransferase
BSC	Best supportive care
CBR	Clinical benefit rate
CD-38	Cluster of differentiation 38
CI	Confidence interval
CR	Complete response
CRi	Complete remission with incomplete recovery
CRp	Complete remission with platelet recovery
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EE	Exploratory efficacy
EHR	Electronic health record
FACT	Functional Assessment of Cancer Therapy
FHAD	Flatiron Health Analytic Database
FISH	Fluorescence in-situ hybridization
HMA	Hypomethylating agent
HR	Hazard ratio
Ig	Immunoglobulin
IMiD	Immunomodulatory drug/agent
IMWG	International Myeloma Working Group
IPTW	Inverse probability of treatment weight
IR	Information request
IRC	Independent Review Committee
ISS	International staging system
ITT	Intent-to-treat
LDAC	Low dose cytarabine
mAb	Monoclonal antibody
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MM	Multiple myeloma
MR	Minimal response
NDA	New drug application

ORR	Overall response rate
OS	Overall survival
PC	Physician's choice
PD	Progressive disease
PFS	Progression-free survival
PI	Proteasome inhibitor
PR	Partial response
PS	Propensity score
PV	Protocol version
QoL	Quality of life
R/R AML	Relapsed/refractory AML
RRMM	Relapsed/refractory multiple myeloma
RWD	Real world data
SAE	Serious adverse event
SAP	Statistical analysis plan
sCR	Stringent complete response
SD	Stable disease
SLAMF7	Signaling lymphocyte activation molecule F7
TEAE	Treatment-emergent adverse event
TP53	Tumor suppressor protein 53
TTP	Time-to-progression
ULN	Upper limit of normal
VGPR	Very good partial response
XPO1	Exportin-1

1. Introduction

1.1 Proposed Indication

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

1.2 Executive Summary

NDA 212306 is primarily based on Part 2 of the phase 2b trial, KCP-330-012 (STORM).

STORM was a multicenter, open-label, single arm trial evaluating selinexor in combination with dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM). Part 2 enrolled 123 patients with RRMM who had received at least 3 prior therapies, including an alkylating agent, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, and a glucocorticoid, and whose disease was considered refractory to at least one PI (i.e., bortezomib and/or carfilzomib), at least one IMiD (i.e., lenalidomide and/or pomalidomide), and an anti-CD38 mAb (i.e., daratumumab). The primary endpoint was overall response rate (ORR; defined as the proportion of patients with a partial response (PR) or better). Key secondary endpoints included duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

Analysis of efficacy is based on 122 patients (modified-intent-to-treat (mITT) population) enrolled in Part 2 of STORM. The primary analysis of safety includes the 123 patients enrolled and treated on Part 2 of STORM. Additional safety analyses include the 79 patients enrolled and treated in Part 1 of STORM, and patients with other advanced hematologic malignancies treated on 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.

Efficacy (STORM Part 2)

- The ORR was 25.4% (95% CI 18.0, 34.1), including 2 patients with sCR, 6 patients with VGPR, and 23 patients with PR (N = 122).

- The median DOR among responders (N = 31) was 4.4 months (range 0.8, 9.0).

Safety (STORM Part 2)

- 23 deaths occurred on or within 30 days of study treatment. Reasons for death included 13 (10.6%) deaths due to disease progression, 10 (8.1%) deaths due to a fatal treatment-emergent adverse event (TEAE).

- All patients experienced at least one TEAE, 93.5% experienced at least one severe (Grade 3–4) TEAE, and 60.2% experienced at least one serious adverse event (SAE).

- Most patients (88.6%) required at least one dose modification due to a TEAE and 28.5% of patients permanently discontinued study treatment because of a TEAE.

2. Issues

2.1 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.

2.2 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 (88.6%) required a dose modification due to a TEAE and over a one-quarter (28.5%) 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.

2.3 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 88.6% the patients in Part 2 of STORM required at least one dose modification due to a TEAE and 28.5% 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.

3. Background

3.1 Multiple Myeloma

Multiple myeloma (MM) is a hematologic malignancy characterized by clonal expansion of plasma cells in the bone marrow and over-production of monoclonal immunoglobulins, leading to impaired hematopoiesis, bone destruction, and renal dysfunction. MM is the second most common hematologic malignancy, accounting for nearly 2% of all new cancer cases and deaths. It is estimated that 32,110 new cases of MM will be diagnosed and 12,960 patients will die from MM in the U.S. in 2019.[1] The median age at diagnosis is 69 years, and the 5-year survival rate is approximately 50%.[2] Significant advances have been made in the treatment of MM in recent decades, however, it is not considered curable, and most patients will eventually relapse and are likely to develop refractory disease. Treatment of RRMM remains challenging. In general, the duration of remission shortens with each subsequent line of therapy, and patients who become refractory to the major classes of available anti-myeloma therapies have very poor outcomes.[3]

3.2 Multiple Myeloma Treatment

Nine drugs are approved specifically for the treatment of RRMM, and four new drugs or biologics have been approved since 2015, including a histone-deacetylase inhibitor, an oral PI, an anti-CD38 mAb and an anti-SLAMF7 mAb. Table 1 shows the drug and biologic regimens specifically approved for the treatment of RRMM.

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) with dex	Accelerated (2013)	MM, at least 2 prior lines, including len and PI	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,	ORR	Single-arm trial ORR: 29%

		including PI and IMiD*		*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, DVd = daratumumab + Vd, ERd = elotuzumab + Rd, EPd = Elotuzumab + Pd
(Source: FDA)

4. Drug Description

Selinexor is a first-in-class, oral inhibitor of the nuclear export protein, exportin 1 (XPO1). The dosing for the proposed indication is selinexor 80 mg orally twice weekly in combination with dexamethasone 20 mg orally twice weekly (on Days 1 and 3), on Weeks 1–4 of a 28-day cycle, until disease progression or unacceptable toxicity.

5. Trial

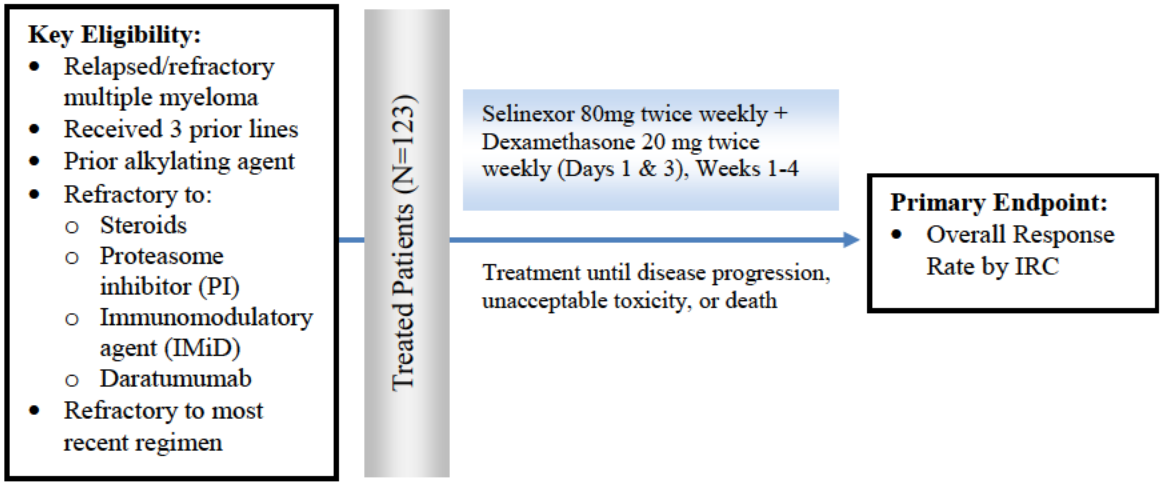
The efficacy and safety of selinexor for the proposed indication was primarily evaluated in Part 2 of study KCP-330-012 (STORM). Patients with triple-class refractory MM were originally included as an exploratory subset of Part 1 of STORM; however, given the approval of daratumumab in 2015, the protocol was subsequently amended to address the changes in the treatment landscape for RRMM. Protocol Amendment 3 (Version 4.0) expanded the study to enroll approximately 130 additional patients with triple-class

refractory MM to Part 2 and designated this population at the mITT population for the primary efficacy analysis.

5.1 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. Treatment was continued until disease progression, unacceptable toxicity, or death. The primary endpoint was ORR by IRC.

Figure 1: STORM Part 2 Study Schema



(Source: FDA)

5.2 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 (Figure 1). Part 1 of STORM primarily enrolled patients who were "quad-exposed" (prior treatment with lenalidomide, pomalidomide, bortezomib, carfilzomib) and "double-class refractory" (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/mm^3 if >50% bone marrow plasma cells), and hemoglobin ≥8.5 g/dL.

The full eligibility criteria for STORM are included in Appendix 10.1.5.

5.3 Study Drug Administration and Schedule

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, were treated on the 8 doses per cycle schedule. Treatment was continued until disease progression, unacceptable toxicity, or death. Dose levels for selinexor dose modifications are shown in Table 2.

Table 2: STORM Dose/Schedule Modifications for Selinexor

	Dose Level	Selinexor Dosing
Dose Increase	1	100 mg twice-weekly (200 mg total per week)
Starting Dose	0	80 mg twice-weekly (160 mg total per week)
Dose Reductions	-1	60 mg twice-weekly (120 mg total per week)
	-2	100 mg total per week: 100 mg once weekly *OR*

		divided as 60 mg and 40 mg on separate days
	-3	80 mg total per week: 80 mg once weekly *OR* divided as 40 mg on separate days
	-4	60 mg total per week: 60 mg once weekly *OR* divided as 40 mg and 20 mg on separate days
	-5	40 mg total per week: 40 mg once weekly *OR* divided as 20 mg on separate days

(Source: KCP-330-012 Clinical Study Report)

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), MR or PR.

5.4 Efficacy Evaluation

Disease response in Part 2 of STORM was assessed per the IMWG 2016 criteria[5] and adjudicated by an IRC. A portion of the responses in Part 1 were assessed per IMWG 2014 criteria.[6] 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.

5.5 Safety Evaluation

Safety evaluation included collection of all adverse events (AEs) and serious AEs (SAEs). Safety assessments included monitoring of hematology and chemistry panels, symptom-directed physical examinations, vital signs, body weight, and determination of ECOG performance status. These assessments were performed at screening, at the start of each treatment cycle, and at the end-of-treatment visit. Additional assessments at

screening included an echocardiogram, 12-lead ECG, full physical examination, ophthalmic exam, urinalysis, and coagulation tests.

Adverse events were coded using the medical dictionary for regulatory activities (MedDRA) version 20.1 and graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

6. Trial Results

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.

6.1 Patient Population

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.

6.1.1 Demographics

Demographics of the patient population are summarized in Table 3. The median age of patients enrolled in STORM (64) for relapsed/refractory disease was younger than the median age at diagnosis for MM (69) in the U.S. Otherwise, basic demographic characteristics were similar to the U.S. population of patients with MM.[2]

Table 3: STORM Demographics

	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)

6.1.2 Baseline Characteristics

The baseline characteristics of patients enrolled and treated on STORM are shown in Table 4. Most patients had an ECOG performance status of 0 or 1, with a median of 1. Overall, 50% of patients had an ISS stage of II or III at diagnosis, but ISS stage was missing for 30.2% of patients (33.3% of patients in Part 2). Poor risk cytogenetic features (del(17p) and/or t(4:14)) were present in 46% of the overall study population and 35% of patients in Part 2. Overall, approximately half of the patients had MM with high-risk features (ISS stage II or III, and del(17p) or t(4;14)).[7]

Table 4: STORM Baseline Disease Characteristics

	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 (2.5)	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)

6.1.3 Prior Therapies

Table 5 summarizes the prior therapies for patients on 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 5: STORM Prior Therapies

	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	4 (5.1)	5 (4.1)	9 (4.5)
≥10	18 (22.8)	31 (25.2)	49 (24.3)
Median Prior Lines of Therapy (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	7 (8.9)	15 (12.2)	22 (10.9)
PD	32 (40.5)	16 (13)	48 (23.8)
SD	17 (21.5)	30 (24.4)	47 (23.3)
MR	9 (11.4)	10 (8.1)	19 (9.4)
≥PR	14 (17.7)	52 (42.3)	66 (32.7)
Prior Daratumumab	21 (26.6)	123 (100)	144 (71.3)
In Last Line of Therapy	12 (15.2)	58 (47.2)	70 (34.7)
As Monotherapy	14 (17.7)	36 (29.3)	50 (24.8)
As Combination Therapy	7 (8.9)	87 (70.7)	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)

6.1.4 Disposition

As of the 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. The stated reasons for discontinuation are summarized in Table 6. Discontinuations due to AEs and deaths within 30 days of study treatment are further discussed in Section 6.3.

Table 6: STORM Part 2 Patient Disposition

Reason for Discontinuation	**Part 2 (N = 123) n (%)**
Disease Progression	59 (55.7)
Adverse Event	31 (29.2)
Withdrawal	7 (6.6)
Physician Decision	4 (3.8)
Other	3 (2.8)
Death	2 (1.9)

(Source: FDA Analysis)

6.2 Efficacy

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 7. 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 7: STORM Part 2 Efficacy Analysis of ORR and DOR

IRC Assessment	
mITT Population (N = 122)	
ORR (≥ PR), n (%); [95% CI] sCR CR VGPR PR	**31 (25.4); [18.0, 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, 9.0 months]**

(Source: FDA Analysis)

6.3 Safety

The safety analysis was primarily performed on the results for patients enrolled and treated on STORM Part 2 (N = 123). Because of the differences in baseline characteristics, prior therapies and the treatment schedule for many of the patients enrolled in Part 1 (N = 79), the safety results for Part 1, Part 2, and the total population (N = 202) are presented side-by-side. Additional safety analyses include results from patients with other advanced hematologic malignancies treated on trial KCP-330-008 (acute myeloid leukemia (AML)), KCP-330-009 (diffuse-large B-cell lymphoma (DLBCL)), and KCP-330-010 (Richter's transformation).

6.3.1 Safety Overview

Treatment with selinexor in combination with dexamethasone on STORM was associated with significant toxicity (Table 8). All patients (100%) enrolled and treated on STORM experienced at least one TEAE. There was a high frequency of severe TEAEs, with nearly all (94.1%) patients experiencing at least one Grade 3 or 4 TEAE and almost two-thirds (58.4%) of patients experiencing at least one serious AE (SAE). Over one-quarter (26.7%) of patients permanently discontinued selinexor due to a TEAE and 18 (8.9%) patients (8 (10.1%) in Part 1 and 10 (8.1%) in Part 2) had a fatal TEAE.

Table 8: STORM Overview of TEAEs

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)

6.3.2 Dose Modifications and Discontinuations

A substantial proportion of patients in STORM required dose modifications or permanent discontinuation of study treatment. As summarized in Table 9, 121 (98.4%) patients in Part 2 experienced at least one dose modification (including dose reduction, dose interruption, or permanent discontinuation of selinexor) due to any cause. A total of 109 (88.6%) patients required at least one dose modification due a TEAE, and 35 (28.5%) patients permanently discontinued selinexor due to a TEAE. Though a slightly lower percentage of patients in Part 1 experienced dose reductions and/or interruptions, 51 (64.6%) of patients in Part 1 received a reduced dosing schedule of 6 doses of selinexor plus dexamethasone per cycle.

Table 9: STORM Part 2 Dose Modifications Due to TEAEs

Action Taken with Selinexor	Part 2 (N = 123) n (%)
Dose modification due to TEAE Dose reduced Dose interrupted Drug discontinued	109 (88.6) 71 (57.7) 84 (68.3) 35 (28.5)
All dose modifications (due to any cause)	121 (98.4)

(Source: Applicant's Response to FDA Information Request Dated January 23, 2019)

Tables 10 and 11 summarize the most frequent TEAEs leading to dose interruption (occurring in ≥2.5% of patients overall) and dose reduction (occurring in ≥1% of patients overall), respectively.

Table 10: STORM TEAEs Leading to Dose Interruption*

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)	20 (16.3)	26 (12.9)
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)	5 (4.1)	6 (3)
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
[*] The numbers in this table were calculated based on the original dataset (ADAE.xpt) submitted to the NDA. The total number of patients experiencing a TEAE leading to dose modification (interruption, reduction, or discontinuation) were updated in the Applicant's Response to FDA Information Request Dated January 23, 2019; however, updated datasets were not provided as of January 28, 2019. Therefore, this table may underrepresent the actual number of patients experiencing a particular TEAE leading to a dose modification.
(Source: FDA Analysis)

Table 11: STORM TEAEs Leading to Dose Reduction[*]

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)	10 (8.1)	14 (6.9)
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	2 (2.5)	0	2 (1)
Hyponatremia	2 (2.5)	1 (0.8)	3 (1.5)

[†]Includes terms fatigue and asthenia
[*] The numbers in this table were calculated based on the original dataset (ADAE.xpt) submitted to the NDA. The total number of patients experiencing a TEAE leading to dose modification (interruption, reduction, or discontinuation) were updated in the Applicant's Response to FDA Information Request Dated January 23, 2019; however, updated datasets were not provided as of January 28, 2019. Therefore, this table may underrepresent the actual number of patients experiencing a particular TEAE leading to a dose modification.
(Source: FDA Analysis)

The most common TEAEs (occurring in ≥ 2 patients overall) leading to discontinuation of study treatment are summarized by preferred term in Table 12.

Table 12: STORM TEAEs Leading to Discontinuation*

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]	4 (5.1)	2 (1.6)	6 (3)

[a] Includes terms fatigue and asthenia
[b] Includes terms sepsis and septic shock
[c] Includes terms mental status changes, confusional state, and delirium
* The numbers in this table were calculated based on the original dataset (ADAE.xpt) submitted to the NDA. The total number of patients experiencing a TEAE leading to dose modification (interruption, reduction, or discontinuation) were updated in the Applicant's Response to FDA Information Request Dated January 23, 2019; however, updated datasets were not provided as of January 28, 2019. Therefore, this table may underrepresent the actual number of patients experiencing a particular TEAE leading to a dose modification.

The most common reasons for discontinuation of study treatment in Part 2 by system organ class (Table 13) include general disorders and administration site conditions

(asthenia, fatigue, and general physical health deterioration), infections and infestations (bronchitis, fungal infection, influenza, pneumonia, sepsis, septic shock, and streptococcal bacteremia), gastrointestinal disorders (diarrhea, dysphagia, nausea, and vomiting), investigations (weight decreased) and blood and lymphatic system disorders (anemia and thrombocytopenia).

Table 13: STORM Part 2 Discontinuations due to TEAEs 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)

* The numbers in this table were calculated based on the original dataset (ADAE.xpt) submitted to the NDA. The total number of patients experiencing a TEAE leading to dose modification (interruption, reduction, or discontinuation) were updated in the Applicant's Response to FDA Information Request Dated January 23, 2019; however, updated datasets were not provided as of January 28, 2019. Therefore, this table may underrepresent the actual number of patients experiencing a particular TEAE leading to a dose modification.
(Source: FDA Analysis)

6.3.3 Deaths within 30 Days of Study Treatment

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. There was insufficient information to support disease progression as the cause of death for 2 patients in Part 1 of STORM. There were 42 on-study deaths in STORM, 19 (24.1%) in Part 1,

and 23 (18.7%) in Part 2. 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). All on-study deaths are summarized in Table 14.

Table 14: STORM Deaths within 30 Days (On-Study Deaths)

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) [a]	10 (8.1) [b]	18 (8.9)
Insufficient information	2 (2.5) [c]	0	2 (0.5)

* Reason for death updated from "unknown" to progressive disease after data cut-off.
[a] Causes of death include dyspnea, influenza, cardiorespiratory arrest (2), subdural hematoma, multiple organ dysfunction syndrome, ascites and plasma cell leukemia, and respiratory failure
[b] Causes of death include pneumonia (2), sepsis (2), subdural hematoma, cardiac disorder, fungal sepsis, multiple organ dysfunction syndrome, respiratory arrest, septic shock
[c] Subjects (b) (6) and (b) (6)
(Source: FDA Analysis)

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. For example, of the 10 deaths due to a TEAE in Part 2, the Applicant designated 2 deaths as "treatment related" (pneumonia and sepsis), and the remaining 8 deaths as "non-treatment related" (pneumonia, sepsis, subdural hematoma, cardiac disorder, fungal sepsis, multiple organ dysfunction syndrome, respiratory arrest, and septic shock). However, because treatment with selinexor is associated with risk of infection, it is notable that 4 of the 8 deaths classified as "non-treatment related" were due to infection. 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 Agency considers all deaths due to a TEAE in this setting to be treatment-related, unless clearly related to other extraneous causes.

6.3.4 Serious Adverse Events

Treatment-emergent serious adverse events (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 15. 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 15: STORM Most Common SAEs (>2%)

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 (3.0)
Febrile neutropenia	3 (3.8)	0	3 (1.5)
Thrombocytopenia	5 (6.3)	3 (2.4)	8 (4.0)
Cardiac disorders			
Cardiorespiratory arrest	2 (2.5)	0	2 (1.0)
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			
Fatigue [a]	3 (3.8)	6 (4.9)	9 (4.5)
General physical health deterioration	0	4 (3.3)	4 (2.0)
Pyrexia	3 (3.8)	3 (2.4)	6 (3.0)
Infections and infestations			
Influenza [b]	5 (6.3)	1 (0.8)	6 (3.5)
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)	5 (4.1)	9 (4.5)
Fall	2 (2.5)	2 (1.6)	4 (2.0)
Metabolism and nutrition disorders			
Dehydration	3 (3.8)	3 (2.4)	6 (3.0)
Hypercalcemia	4 (5.1)	0	4 (2.0)
Hyponatremia	2 (2.5)	3 (2.4)	5 (2.5)
Psychiatric disorders			
Mental status changes [g]	6 (5.1)	8 (6.5)	14 (6.9)
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 (2.0)

[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)

6.3.5 Adverse Events

All patients in STORM experienced at least one TEAE. The most common TEAEs of any grade that occurred in at least 5% of patients overall or in either part of STORM are shown in Table 16. 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 (79.7%), weight decreased (48.8%), decreased appetite (53.7%), hyponatremia (35%), and dyspnea (22%).

Table 16: STORM Most Common TEAEs (≥5%)

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]	8 (10.1)	11 (8.9)	19 (9.4)

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]	62 (78.4)	98 (79.7)	160 (79.2)
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]	2 (2.5)	11 (8.9)	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)	11 (8.9)	16 (7.9)
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]	16 (20.3)	13 (10.6)	29 (11.4)
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]	14 (17.7)	21 (17.1)	35 (17.3)
Insomnia	11 (13.9)	19 (15.4)	30 (14.9)
Renal and urinary disorders			
Renal impairment [m]	4 (5.1)	7 (5.7)	11 (5.4)
Respiratory, thoracic and mediastinal disorders			
Cough [n]	14 (17.7)	20 (16.3)	34 (16.8)
Dyspnea [o]	23 (29.1)	27 (22)	50 (24.8)
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
[m] Includes terms cough and productive cough
[o] Includes terms dyspnea, dyspnea at rest, and dyspnea exertional
(Source: FDA Analysis)

Grade 3 or 4 TEAEs are events that are severe, debilitating, or life-threatening. Nearly all (approximately 94%) patients treated on 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 overall or in either part of STORM are shown in Table 17. 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 (25.2%), and hyponatremia (20.3%).

Table 17: STORM Most Common Grade 3 or 4 TEAEs (≥5%)

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)	31 (25.2)	46 (22.8)
General physical health	0	7 (5.7)	7 (3.5)

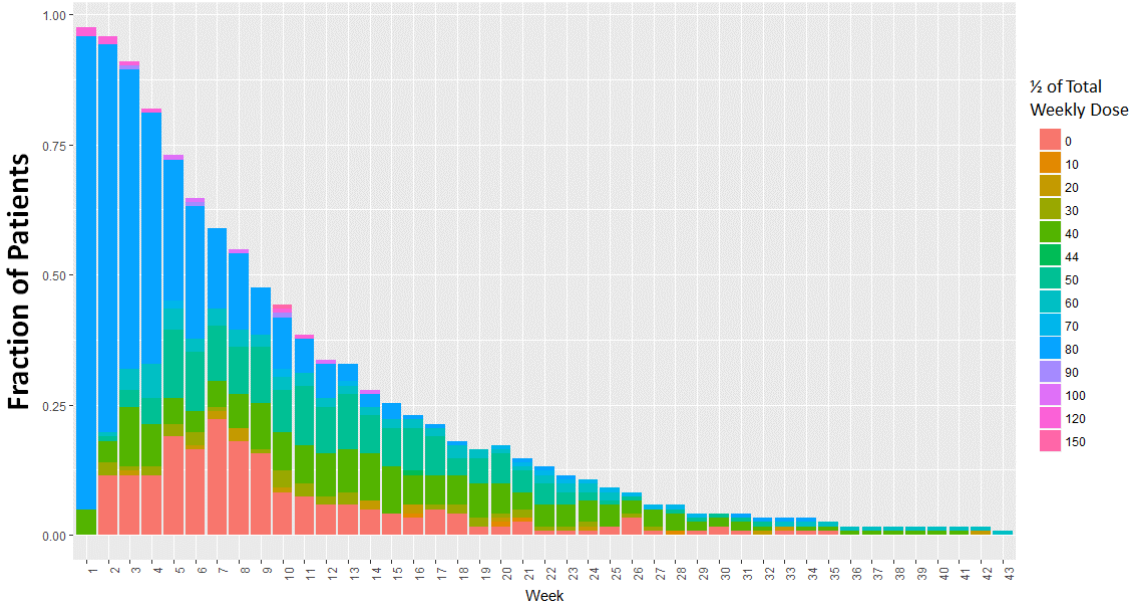
deterioration			
Infections and infestations Influenza [b] Pneumonia [c] Sepsis [d]	 4 (5.1) 4 (5.1) 1 (1.3)	 1 (0.8) 11 (8.9) 7 (5.7)	 5 (2.5) 15 (7.4) 8 (4)
Injury, poisoning and procedural complications Fracture [e]	3 (3.8)	6 (4.9)	9 (4.5)
Metabolism and nutrition disorders Decreased appetite Hypercalcemia Hypercreatinemia Hyperglycemia Hypokalemia Hyponatremia	 4 (5.1) 4 (5.1) 4 (5.1) 9 (11.4) 0 19 (24.1)	 5 (4.1) 0 0 6 (4.9) 7 (5.7) 25 (20.3)	 9 (4.5) 4 (2) 4 (2) 15 (7.4) 7 (3.5) 44 (21.8)
Psychiatric disorders Mental status changes [f]	8 (10.1)	7 (5.7)	15 (7.4)
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 septic shock
[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)

6.3.6 Exposure-Response Analysis of Adverse Events

As described in Section 6.3.1, the proposed 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 was associated with significant toxicity as 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, 88.6% of patients had a TEAE that resulted in dose modification (Table 9), and 77.0% of patients had 2 or more dose reductions. The fraction of patients at each treatment level over time in Part 2 of STORM is shown in Figure 2. It is important to note that the treatment (dose) level shown in Figure 2 is half of the total weekly dose and the figure excludes missed doses and dose-modifications due to progressive disease.

Figure 2: STORM Part 2 Relationship of Selinexor Treatment Duration and Fraction of Patients at Each Selinexor Treatment Level (N=122)



(Source: FDA Analysis)

As shown in Figure 2, the fraction of subjects 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 high doses of selinexor was also observed in the Phase 1 clinical trial (KCP-330-001) cohorts that compared selinexor 45 mg/m^2 to selinexor 60 mg/m^2 twice weekly with dexamethasone 20 mg, as described in Section 7.1. A median (range) duration of treatment of 15 days (1–93) was observed in the selinexor 60 mg/m^2 arm with dexamethasone compared to 115 days (8–365) in the selinexor 45 mg/m^2 arm with dexamethasone.

Additionally, exposure-response analysis indicates that there is a relationship between higher selinexor exposure and 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 from studies KCP-330-001, KCP-330-008, KCP-330-009, KCP-330-010, and KCP-330-012 is shown in Table 18.

Table 18: 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), suggesting that lower doses may be better tolerated. See Appendix 10.2 for further analysis results and details.

7. Supportive Data

7.1 Phase 1 Trial KCP-330-001

Supportive data for the NDA includes results from KCP-330-001, a phase 1, open-label, dose escalation and dose expansion study that evaluated the pharmacokinetics, pharmacodynamics, and safety and tolerability of selinexor in patients with advanced hematologic malignancies. As summarized in Table 19, there were 8 arms based on the type of hematologic malignancy, and 11 dose schedules across the arms. Arms 1, 2, and 7 included dose escalation cohorts.

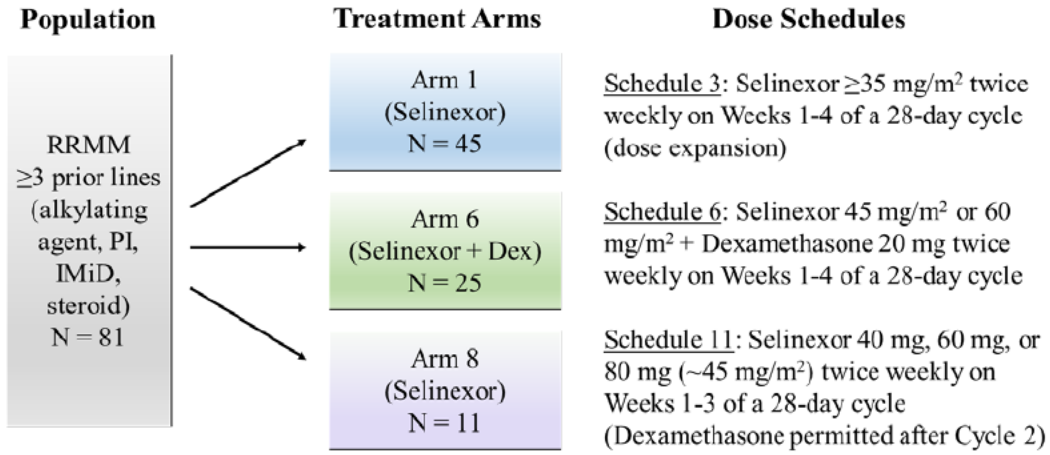
Table 19: KCP-330-001 Study Arms

Arm	Population	Regimen	Study Phase	Schedule(s)
1	DLBCL, **MM**	Selinexor	Dose Escalation Dose Expansion	1, 2, 3, 4, 5, 7, 8 3
2	AML	Selinexor	Dose Escalation Dose Expansion	1, 2, 3, 5, 7 3, 8, 10
3	PTCL, CTCL	Selinexor	Dose Expansion	3
4	CML	Selinexor	Dose Expansion	3
5	ALL	Selinexor	Dose Expansion	3
6	**MM**, WM	Selinexor + Dexamethasone	Dose Expansion	6
7	NHL, DLBCL	Selinexor + Rituximab	Dose Escalation Dose Expansion	9
8	**MM**	Selinexor	Dose Evaluation	11

(Source: FDA)

Patients with MM were included on Arms 1, 6, and 8 (Figure 3). Patients on Arms 1 and 8 received selinexor monotherapy, and patients on Arm 6 received selinexor in combination with dexamethasone. Of note, patients on Schedule 11 (Arm 8) were permitted to receive dexamethasone as a concomitant medication after Cycle 2.

Figure 3: KCP-330-001 RRMM Cohorts



(Source: FDA)

7.1.1 Limited Activity of Single-Agent Selinexor in Patients with RRMM

Of the 81 patients with RRMM treated across the dose ranges on study KCP-330-001, only 7 (8.6%) patients responded, including one patient with sCR and 6 patients with PR (Table 20). Most patients experienced stable or progressive disease.

Table 20: KCP-330-001 Best Overall Response in Patients with MM

Best Overall Response	**MM (N = 81) n (%); (95% CI)**
ORR sCR CR PR	**7 (8.6); (4, 17)** 1 (1.2) 0 6 (7.4)
MR	13 (16.0)
SD	29 (35.8)
PD	20 (24.7)
Clinical Progression	1 (1.2)
Not Evaluable/Missing	11 (13.6)

(Source: FDA)

The ORR for patients treated with selinexor in combination with dexamethasone was 24% (Table 21), which is similar to the response rate observed in STORM (25.4%);

however, there was only 1 response (PR) among the 56 patients who received selinexor alone (ORR 1.8%). Of note, this patient received dexamethasone as a concomitant medication, which was permitted on Schedule 11 after Cycle 2. Moreover, there was a lack of responses even at doses of selinexor that are higher than the recommended phase 2 dose studied in STORM.

Table 21: KCP-330-001 Responses in Patients with MM by Regimen

Response	**MM (N = 81) n (%); (95% CI)**
Selinexor Monotherapy (N = 56)	
ORR	**1 (1.8)**
sCR	0
CR	0
PR	1 (1.8) *
Sd Combination (N = 25)	
ORR	**6 (24); (9, 45)**
sCR	1 (4%)
CR	0
PR	5 (20%)

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

In contrast, selinexor did demonstrate some single agent activity in patients with other advanced hematologic malignancies treated on KCP-330-001 (Table 22).

Table 22: KCP-330-001 Selinexor Activity in Advanced Hematologic Malignancies

Disease Type	**ORR, n (%)**	**Response Categories**
DLBCL (N = 58) *	12 (20.7)	5 CR, 7 PR
NHL (N = 27)	9 (33.3)	1 CR, 8 PR
AML (N = 95)	11 (11.6)	4 CR, 3 CRi, 4 PR
CLL (N = 16)	1 (6.3)	1 PR
MM (N = 56)	1 (1.8)	1 PR

*Selinexor in combination with rituximab
Abbreviations: DLBCL = diffuse large B-cell lymphoma, NHL = non-Hodgkin's lymphoma, AML = acute myeloid leukemia, CLL = chronic lymphocytic leukemia, MM = multiple myeloma, CRi = complete remission with incomplete count recovery.
(Source: FDA)

7.1.2 Challenges in Isolating the Treatment Effect of Selinexor

The data from study KCP-330-001 suggests there is likely synergy between selinexor and dexamethasone given the lack of response in patients with RRMM treated with selinexor monotherapy; however, it is difficult to determine the contribution of dexamethasone to the treatment effect. Historical trials of high-dose dexamethasone demonstrated response rates between 18–27% in patients with RRMM and higher response rates in patients with newly diagnosed MM (Table 23). Although these trials evaluated higher doses of dexamethasone than the doses administered in combination with selinexor on STORM, there is data to suggest that the difference in response to high-dose dexamethasone (HD-dex) and low-dose dexamethasone (LD-dex) may not be that large.[8] However, it is difficult to extrapolate these results to the current era of MM therapy in which patients receive multiple lines of therapy, many of which include dexamethasone as a backbone of standard therapy. The more recent MM-003 trial (enrollment between 2011 and 2012) conducted to support approval of pomalidomide, compared pomalidomide in combination with low-dose dexamethasone to high-dose dexamethasone (HD-dex) in patients with RRMM. Patients in MM-003 received a median of 5 prior lines of therapy, and all patients had received prior dexamethasone, but were not refractory to dexamethasone. The response rate to HD-dex in this trial was 10% based on Investigator assessment, and 4% by IRC assessment.

Table 23: Activity of Dexamethasone in Patients with MM

Population	Trial/Regimen	Response Rate	Response Definition	Reference
Relapsed/Refractory				
RRMM	HD-dex*	27% (refractory), 21% (relapsed)	75% ↓ tumor mass, Bence-Jones protein disappearance	Alexanian *et al*. Ann Int Med (1986)[9]
Relapsed MM, 1-3 prior lines	HD-dex vs. bortez	18% (HD-dex arm)	EBMT Criteria	Richardson *et al*. NEJM (2005)[10]
RRMM, failed bortez and len	HD-dex vs. pom/dex	10% (HD-dex arm)	EBMT or IMWG 2006 Criteria	San Miguel *et al*. Lancet Oncol (2013)[11]
Newly Diagnosed				
NDMM	HD-dex	43%	75% ↓ serum M-protein, Bence-Jones protein	Alexanian *et al*. Blood (1992)[12]

			disappearance, marrow plasmacytosis ↓ to <5%	
NDMM	HD-dex vs. thal/HD-dex	46%	EBMT criteria	Rajkumar *et al*. J Clin Oncol (2008)[13]
NDMM	HD-dex	50%	IMWG 2006 Criteria	Sinha *et al*. Brit J Hematol (2009)[14]

* HD-dex = high-dose dexamethasone (40 mg or 20 mg/m2 x 4 days beginning on Days 1, 9, and 17 of a 28-day cycle)
(Source: FDA)

7.1.3 Dose Finding in KCP-330-001

The proposed starting dose of selinexor in combination with dexamethasone was based on efficacy and safety data from KCP-330-001, a phase 1, open-label, dose-escalation and expansion study in patients with advanced hematologic malignancies, including RRMM. As described in Section 7.1.1, 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 24.

Table 24: KCP-330-001 Best Overall Response by Dose in Arm 1

Best Overall Response	**Dose (mg/m2)**										**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			1								1 (2.2)

Progression											
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)

Selinexor doses of 45 mg/m^2 or 60 mg/m^2 in combination with dexamethasone 20 mg were administered on Days 1 and 3 of each week in Schedule 6, which enrolled 25 patients with RRMM. The ORR and duration of exposure for these patients are shown in Table 25.

Table 25: 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 (MM 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 25, 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. The recommended Phase 2 dose for Study KCP-330-012 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.

7.2 Acute Myeloid Leukemia Trial

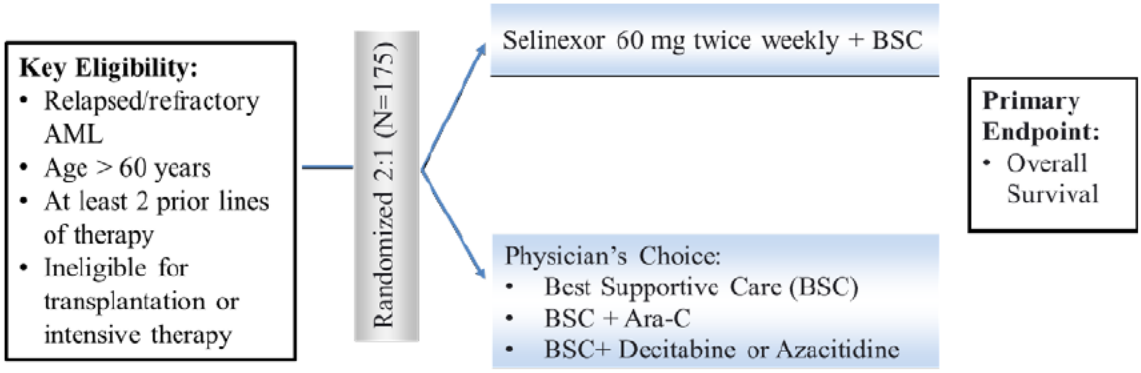
Study KCP-330-008 (SOPRA trial) was a randomized, open-label, phase 2 trial of selinexor versus physician's choice (PC) in patients aged ≥ 60 years with relapsed or refractory AML (R/R AML) who were ineligible for intensive chemotherapy and/or

transplantation.

7.2.1 Trial Design

The primary objective of SOPRA was to determine the overall survival of selinexor compared to PC. Eligible patients were those of age ≥ 60 years with relapsed or refractory AML (excluding APL) who had never undergone and were not eligible for stem cell transplantation and deemed unfit for intensive chemotherapy (Figure 4).

Figure 4: KCP-330-008 (SOPRA) Study Schema



(Source: FDA)

Per Protocol Version 5.1 (PV 5.1), patients must have received at least 2 prior lines of therapy. Prior therapy must have included at least 1 regimen including Ara-C and at least 1 regimen including a hypomethylating agent. In Protocol Version 5.0 (PV 5.0), patients must have received at least 1 prior line of therapy, and in protocol versions prior to 5.0 (PV < 5.0), patients must have received 1 prior line of therapy (Table 26). Patients were randomized 2:1 to receive either selinexor or PC. Stratification factors included: (1) duration of first CR on prior therapy (> 6 months versus ≤ 6 months or never achieved CR); (2) age < 70 versus age ≥ 70 years; (3) peripheral leukemic blast counts ≥ 10,000/μL versus < 10,000/μL.

Table 26: KCP-330-008 Protocol Amendments

	Protocol Versions < 5.0	**Protocol Version 5.0**	**Protocol Version 5.1**
Patient Inclusion/Exclusion	1 prior line of therapy only	At least 1 prior line of therapy	At least 2 prior lines of therapy
Required Prior Therapy	Must have received Ara-C or HMA	Must have received an HMA	Must have received Ara-C and an HMA

Selinexor Dose	55 mg/m^2 (~90 mg)	Fixed dose of 60 mg	Fixed dose of 60 mg
Analysis Plan	-	Revised ITT population to exclude patients treated with ~55 mg/m^2	-

Abbreviations: Ara-C = cytarabine, HMA = hypomethylating agent
(Source: FDA)

For protocol versions < 5.0, the dose of selinexor was 55 mg/m^2 (approximately 95 mg). The dose was changed to a flat based dose of 60 mg (approximately 35 mg/m^2) with protocol version 5.0 due to a signal of increased sepsis SAEs associated with selinexor.

PC was selected by the investigator and was limited to 1 of 3 salvage regimens: best supportive care (BSC), BSC + Ara-C, or BSC + hypomethylating agent (HMA; either decitabine or azacitidine). The PC regimens are listed below:

- Best supportive care: blood product transfusions, antimicrobials, growth factors as needed, and hydroxyurea.
- BSC + low dose Ara-C (LDAC): LDAC 20 mg twice daily subcutaneously on Days 1–10/14 to be repeated at 28- to 42-day intervals.
- BSC + HMA:
  - Azacitidine 75 mg/m^2 by subcutaneous injection daily on Days 1–7 or Days 1–5 and 8–9, repeated at 28-day intervals *OR*
  - Decitabine 20 mg/m^2 intravenously on Days 1–5 or Days 1–10, repeated at 28-day intervals.

Treatment was to continue until disease progression, unacceptable toxicity, or patient withdrawal.

Overall survival (OS) was the primary endpoint. OS was calculated from the date of randomization until the date of death. The stratified log-rank test, using the strata included for randomization, was used to test the null hypothesis that the OS distributions are the same for both treatment groups versus the alternative hypothesis that the duration of OS for the selinexor + BSC treatment arm is longer than the group treated with PC. The hazard ratio for each treatment group was estimated from a Cox proportional hazards model stratified by the randomization factors. Disease response was assessed according to International Working Group Criteria.[15]

The study initially planned to enroll 150 patients, but this was increased in PV 5.0 to enroll an additional 171 patients. The ITT population was changed to only include those enrolled on or after protocol version 5.0. The sample size was designed to have 80%

power to detect an improvement in median OS with selinexor of 5.2 months compared to 3.0 months with PC. Patients not evaluated as part of the ITT population (those enrolled prior to PV 5.0) were included in analyses defined as the exploratory efficacy (EE) population. The safety population included any subject who received study treatment.

7.2.2 Trial Results

In total, 317 patients were enrolled and randomized (216 to selinexor and 101 to PC). The ITT population (PV ≥5.0) included 175 patients (118 randomized to selinexor and 57 to PC). Of the 57 patients randomized to PC in the ITT population, 6 received BSC alone, 22 received BSC + Ara-C, 16 received BSC+ HMA, and 13 received no treatment. The safety population included 297 patients. The baseline patient characteristics are included in Table 27.

Table 27: KCP-330-008 Baseline Characteristics (ITT Population)

	Selinexor 60 mg (N=118) n (%)	**Physician's Choice (N= 57) n (%)**	**Total (N=175) n (%)**
Sex			
Male	72 (61)	41 (72)	113 (65)
Female	46 (39)	16 (28)	62 (35)
Age			
Median (range)	73 (60 – 94)	75 (60 – 87)	74 (60 – 94)
ECOG Score			
0	29 (25)	8 (14)	37 (21)
1	67 (57)	24 (42)	91 (52)
2	16 (14)	11 (19)	27 (15)
Missing	6 (5)	14 (25)	20 (11)
Disease Characteristics			
Prior MDS	13 (11)	3 (5)	16 (9)
TP53 Mutations	14 (12)	3 (5)	17 (14)
ANC < 0.5 x 10^9/L	50 (42)	12 (21)	62 (35)

(Source: FDA Analysis)

The treatment arms were well balanced for the stratification factors, however, there were some differences in baseline disease characteristics. Patients in the selinexor arm were more likely to have ECOG performance status score of 0–1 compared to the PC arm (81% vs. 56%). More patients in the selinexor arm had prior MDS (11% vs. 5%), TP53

mutations (12% vs. 5%), and ANC less than 0.5 x 10^9/L (42% vs. 21%). There were also imbalances in the number of patients who were randomized but not treated (1.7% in the selinexor arm compared with 21% in the PC arm).

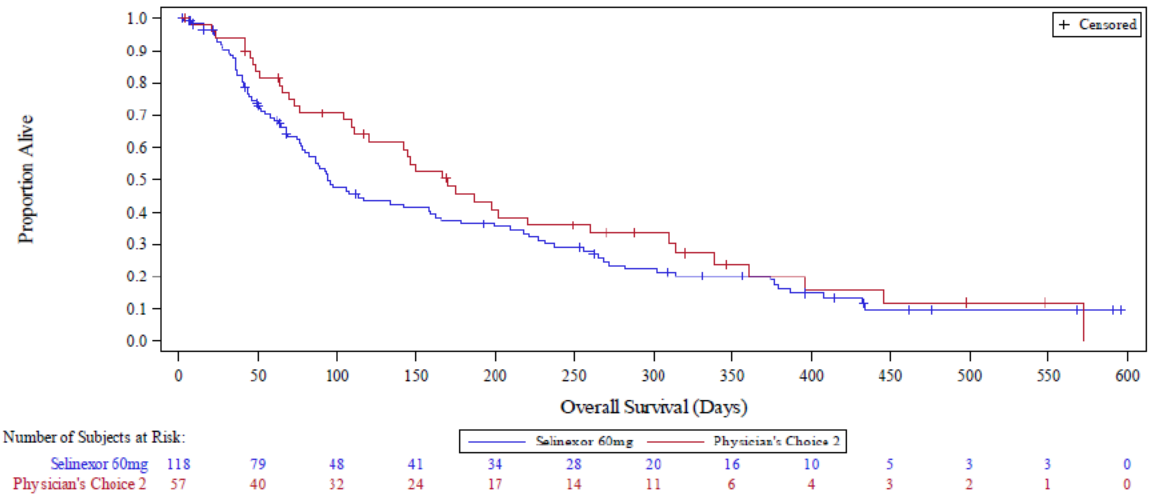
The OS results showed a trend towards a worse survival with selinexor compared with PC. The hazard ratio (HR) was 1.18 (95% CI: 0.79, 1.75) with a median OS of 94 days (95% CI: 78, 158) in the selinexor arm compared to 170 days (95% CI: 110, 220) in the PC arm (Table 28 and Figure 5).

Table 28: KCP-330-008 Overall Survival Results

	Selinexor 60 mg (N=118)	**Physician's Choice (N= 57)**
OS (days), median (95% CI)	94 (78, 158)	170 (111, 220)
HR (95% CI)	1.18 (0.79, 1.75)	

(Source: FDA Analysis)

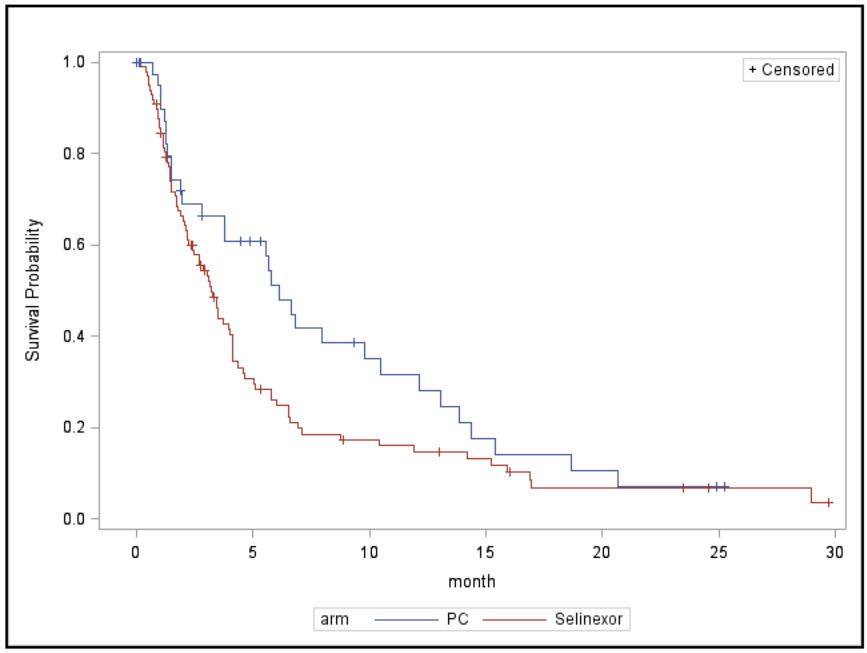
Figure 5: KCP-330-008 Survival Curve (Protocol Version 5.0)



(Source: FDA Analysis)

A similar trend was observed in the EE population (patients enrolled before PV 5.0). The HR was 1.42 (95% CI: 0.91, 2.22) with a median OS of 97 days (95% CI: 68, 125) in the selinexor arm compared to 187 days (95% CI: 85, 319) in the PC arm (Figure 6).

Figure 6: KCP-330-008 Survival Curve (Protocol Version <5.0)



(Source: FDA Analysis)

The overall response rates are included in Table 29.

Table 29: KCP-330-008 Best Overall Response Rates

	Selinexor 60 mg (N=118) n (%)	**Physician's Choice (N= 57) n (%)**
Complete Remission	6 (5)	0
Complete Remission with Incomplete Recovery (CRi)	8 (7)	2 (4)
Complete Remission with Platelet Recovery (CRp)	0	0
Partial Response	2 (2)	3 (5)
Stable Disease	44 (37)	18 (32)
Progressive Disease	12 (10)	6 (11)
Not evaluable	4 (3)	2 (4)
Unknown/Missing*	42 (36)	26 (46)

*Patients did not have at least one efficacy assessment
(Source: FDA Analysis)

The safety results for the ITT population are summarized in Table 30.

Table 30: KCP-330-008 Safety Overview

	Selinexor 60 mg (N = 115) n (%)	**Physician's Choice (N = 45) n (%)**
Treatment-emergent adverse event (TEAE)	115 (100)	42 (93)
Serious TEAE	92 (80)	30 (67)
TEAE leading to treatment withdrawal	54 (47)	9 (20)
TEAE leading to death	23 (20)	9 (20)

(Source: FDA Analysis)

The toxicity profile observed with selinexor in patients with R/R AML was similar to that observed in patients with RRMM in Study KCP-330-012. The most frequent TEAEs associated with selinexor in patients with R/R AML were nausea, vomiting, diarrhea, decreased appetite, fatigue, anemia, thrombocytopenia, and hyponatremia.

Of note, although selinexor resulted in higher rates of remission than PC, OS was worse in the selinexor arm. Disparate response and survival trends can be observed with therapies that have significant toxicity. In this situation, the benefits from anti-tumor activity are abrogated by the toxicity. The results of this study of selinexor in patients with R/R AML underscores the importance of randomized controlled trials.

7.3 Real World Data

The Applicant's NDA submission included a retrospective observational study (Study KS-50039) that attempted to characterize the survival distribution of patients similar to those in STORM Part 2 using electronic health record (EHR) data, also referred to as real-world data (RWD) in this document. A second objective of study KS-50039 was to use the survival distribution obtained from the RWD as a comparator to the survival distribution of STORM Part 2 patients.

Upon review of the submitted RWD and analyses, FDA concludes the following:

- The analyses were not pre-specified, and the study has major methodological issues, including selection bias, misclassification, confounding, missing data, and immortal time bias
- The RWD are not comparable to those obtained in Part 2 of STORM
- The survival estimates obtained from the RWD do not estimate survival of the population enrolled in Part 2 of STORM
- Direct comparison of the survival estimates obtained from the RWD and Part 2 of STORM provide biased estimates of treatment effect; differences in the study arms

are likely to result in longer OS in STORM compared to the Flatiron Health Analytic Database (FHAD) cohort

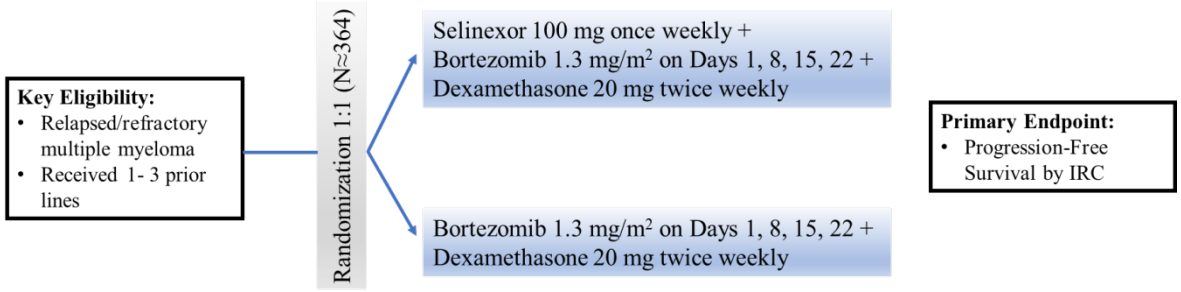
Thus, the FDA concludes that the evidence generated from the RWD analysis is not adequate to provide context/comparison for the overall survival observed in the STORM patients. This conclusion is based primarily on the lack of comparability between the STORM and FHAD treatment groups. Further, FDA's analysis finds that post-hoc strategies to create greater comparability across cohorts were inadequate and resulted in very limited sample size and unstable estimates.

Detailed analysis of KS-50039 is in Appendix 10.1.

7.4 Phase 3 Trial (BOSTON)

The Applicant is conducting a randomized phase 3 trial (BOSTON) of selinexor in combination with bortezomib and dexamethasone compared to bortezomib and dexamethasone alone (Figure 7). Eligible patients are those with RRMM who have received 1–3 prior lines of therapy. Approximately 364 patients will be randomized 1:1 to either arm. The primary endpoint is PFS as assessed by an IRC. The trial has completed accrual and topline data is expected in Q4 of 2019, with a regulatory submission planned in 2020.

Figure 7: Phase 3 Trial (BOSTON) Study Schema



(Source: FDA)

8. Summary

8.1 Conclusions

- In the pivotal study, KCP-330-012 (STORM) Part 2, the combination of selinexor and dexamethasone demonstrated limited efficacy and significant toxicity in patients with RRMM.

- The ORR was 25.4% (95% CI 18.0, 34.1), with a median DOR of 4.4 months (range 0.8, 9.0) among the 31 responders out of a total of 122 patients. Responses included 2 patients with sCR and 6 patients with VGPR; however, most patients (23/31) who responded only achieved a PR.

- Selinexor-dexamethasone was associated with significant toxicity in this population of patients with RRMM. In Part 2 of STORM, all patients (100%) experienced at least one TEAE, 93.5% experienced at least one severe (Grade 3-4) TEAE, 60.2% experienced at least one SAE, and 8.1% experienced a fatal TEAE. The most common TEAEs (occurring in ≥ 30% of patients) were anemia, leukopenia, neutropenia, thrombocytopenia, diarrhea, nausea, vomiting, fatigue, weight decreased, decreased appetite, and hyponatremia. The most common Grade 3-4 TEAEs (occurring in ≥ 20% of patients were anemia, neutropenia, thrombocytopenia, fatigue, and hyponatremia. The most common SAEs (occurring in ≥ 5% of patients) were pneumonia, sepsis, and mental status changes. Over one-quarter (26.8%) of patients discontinued study treatment due to a TEAE. Fatal TEAEs included pneumonia (2 patients), sepsis/septic shock (4 patients), and subdural hematoma, cardiac disorder, respiratory arrest and multiple organ dysfunction syndrome (1 patient each).

- The proposed starting dose of selinexor 80 mg BIW is not well tolerated, as evidenced by the high rate of dose modification due to TEAEs, as well as the frequent dose reductions early during treatment on the STORM trial. The correlation between patient exposure and the occurrence of TEAEs such as thrombocytopenia, neutropenia, hyponatremia, and fatigue, suggest that increased exposure to selinexor leads to increased adverse events. These relationships also suggest that a lower starting dose may impart a lower rate of TEAEs and better tolerability.

- Given the limited efficacy and significant toxicity demonstrated in this population, it is unclear whether treatment with selinexor-dexamethasone provides a clinically meaningful benefit that outweighs the risks of treatment. The limitations of interpreting safety and efficacy from a single arm trial, and lack of single agent activity of selinexor coupled with historical data showing activity of dexamethasone in RRMM, add to the challenges in interpreting the results of the pivotal study in

support of the proposed indication.

- The RWD analyses of the FHAD population were not prespecified and have major methodological issues. The results of Study KS-50039 are difficult to interpret due these limitations, and therefore, are not acceptable as supportive evidence for the NDA.

8.2 Draft Discussion Topics

- Are the results of KCP-330-012 (STORM) conclusive enough to allow for an adequate assessment of the safety and efficacy of Selinexor in the proposed patient population?

- Do the results of KCP-330-012 (STORM) demonstrate that treatment with Selinexor provides a benefit that outweighs the risks from the treatment?

8.3 Draft Voting Question

Should the approval of selinexor be delayed until results of the randomized phase 3 trial, BOSTON, are available?

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10. Appendices

10.1 Real World Data, Study KS-50039

10.1.1 Background

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 10.1.8.

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

10.1.2 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 10.1.9 for full eligibility criteria for STORM Part 2) , and the selection steps used to identify the FHAD cohort are shown in Figure 8. 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.

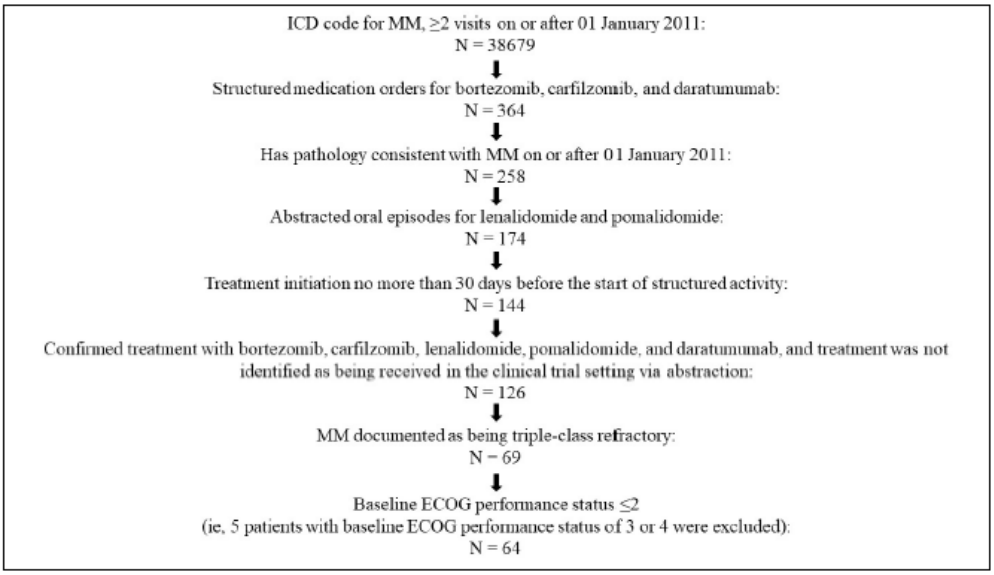
Table 31: Selected Eligibility Criteria for STORM and FHAD

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 8: 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)

10.1.3 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	

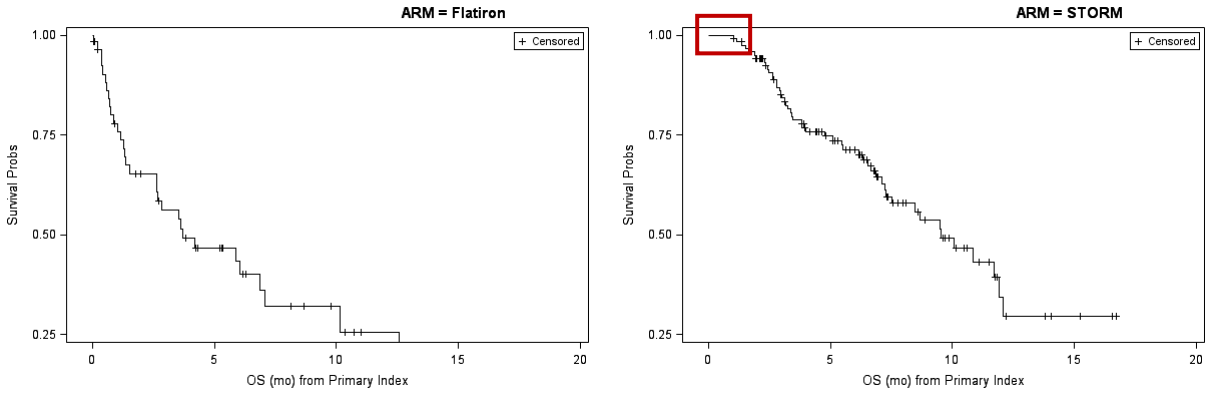
(Source: Applicant's KS-50039 Study Report Dated August 6, 2018)

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 9), 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 9).

Figure 9: Unadjusted OS by Study Population



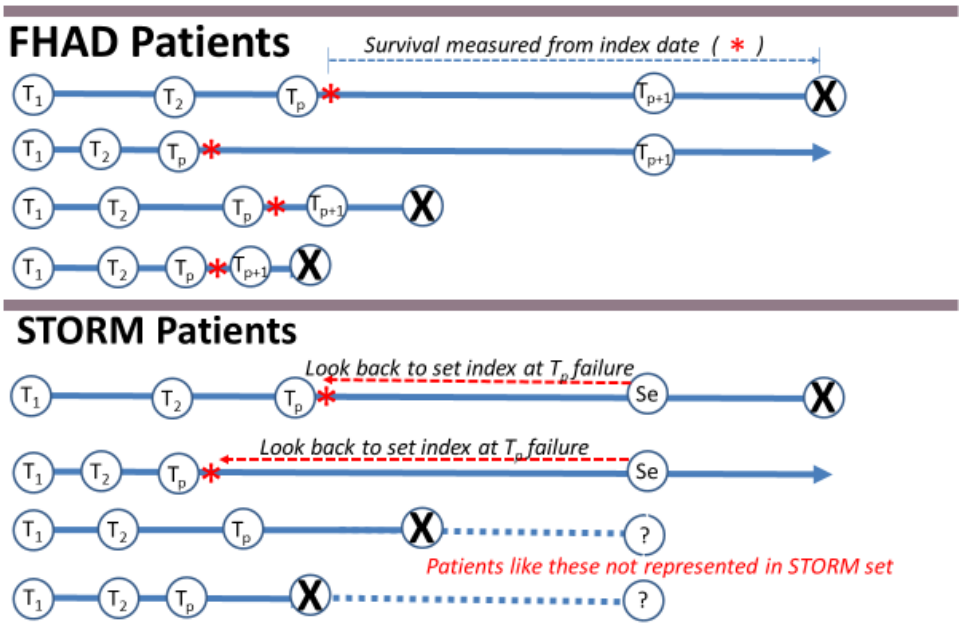
Note: Red box represents minimum level of immortal time bias.
(Source: FDA Analysis)

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 10). 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 9 above).

Figure 10: Immortal Time/Selection Bias



(Source: FDA)

In Figure 10 (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.

10.1.4 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 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 (9.32)	63.8 (9.30)
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 refractory prior to index date, n (%)	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 Type		
IgA or IgM, n (%)	16 (25.0)	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 (9.0)
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.

10.1.5 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 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 11.

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)

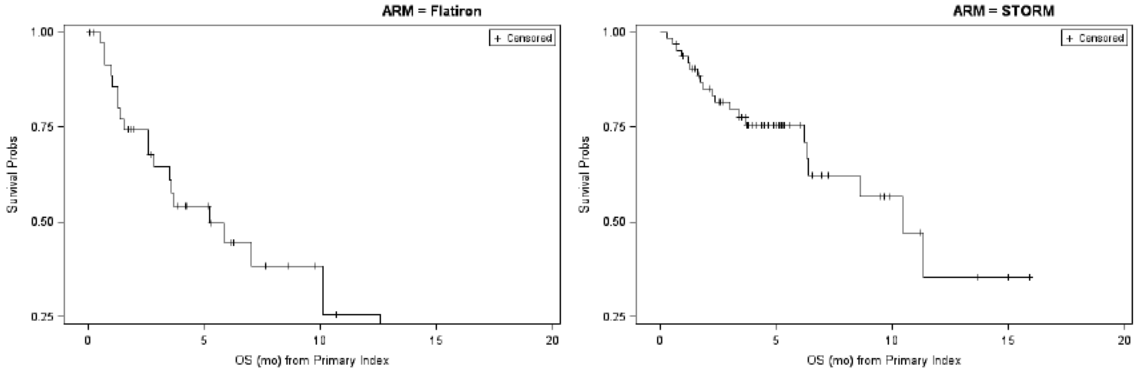
(Source: FDA Analysis)

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 11: 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

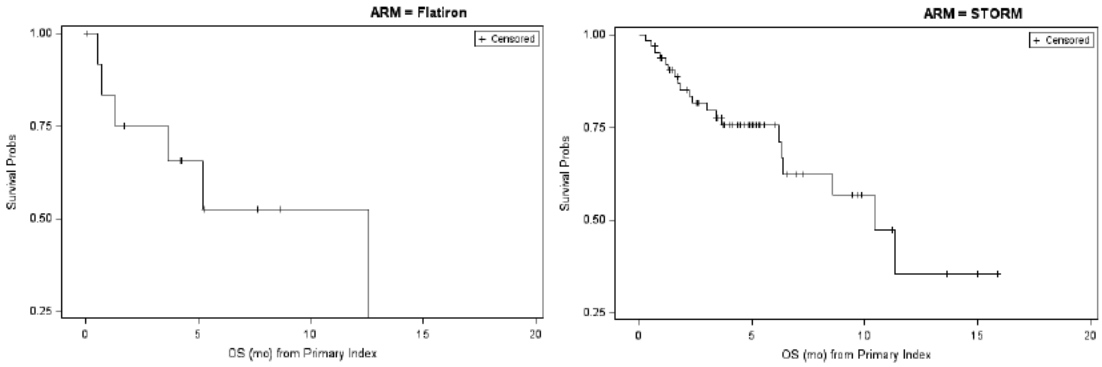
When the data set is modified to meet these three criteria, the number of eligible patients in the FHAD set becomes 13. This data set is likely too small to be representative and the analysis is underpowered to show a difference between the study groups. FDA analysis using the 13 patients from FHAD and 64 patients from STORM is shown in Table 37 and Figure 12. 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 12: Kaplan-Meier Curves for OS Using Updated Index Date and Selection Criteria



(Source: FDA Analysis)

10.1.6 RWD 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.

10.1.7 RWD References

Austin, Peter C. "Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples." *Statistics in medicine*28.25 (2009): 3083-3107.

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Stuart, Elizabeth A. "Matching methods for causal inference: A review and a look forward." *Statistical science: a review journal of the Institute of Mathematical Statistics* 25.1 (2010): 1.

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Wang, Shirley V., et al. "Reporting to improve reproducibility and facilitate validity assessment for healthcare database studies V1. 0." *Pharmacoepidemiology and drug safety* 26.9 (2017): 1018-1032.

10.1.8 RWD Information Request History

Table 38: 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)

10.1.9 STORM 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 glucocorticoid. 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.

10.2: Exposure-Response Analyses for Adverse Events

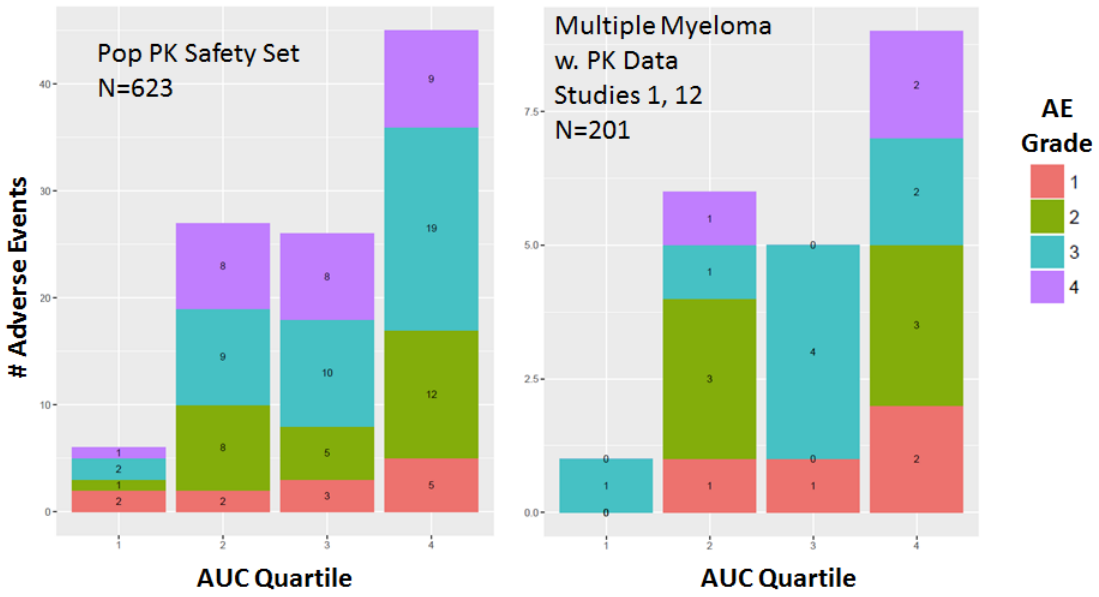
An exposure-response analysis for safety was conducted for the following adverse events from the ISS:

- 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 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) and the MM patient population (N = 201 with PK, studies KCP-330-001 and KCP-330-012). The time to the first event 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 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 13–22 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.

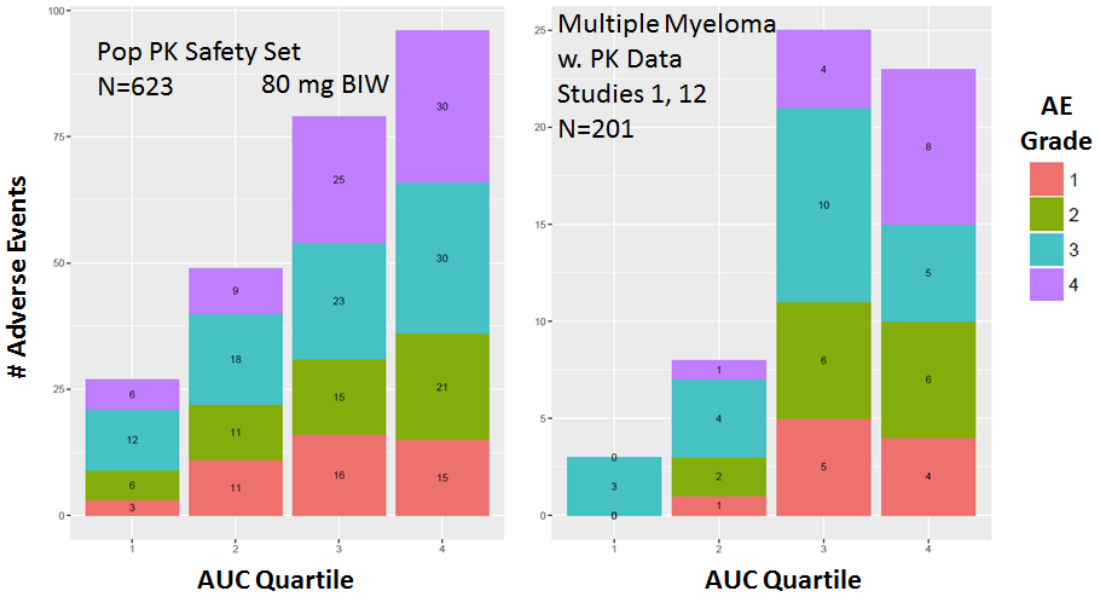
For each of the following graphs (Figures 13–22), the y-axis is the number of subjects with the adverse event. The grade of the adverse event refers to the grade at the first occurrence for that individual.

Figure 13: Exposure-Response Relationship for Neutropenia and Decreased Neutrophil Count



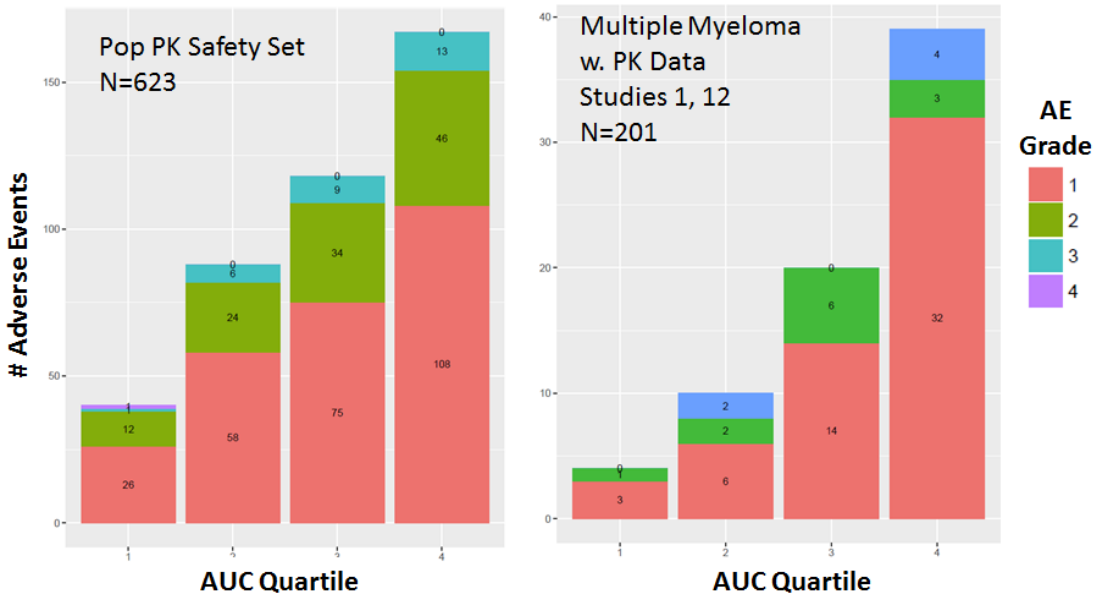
(Source: FDA Analysis)

Figure 14: Exposure-Response Relationship for Thrombocytopenia



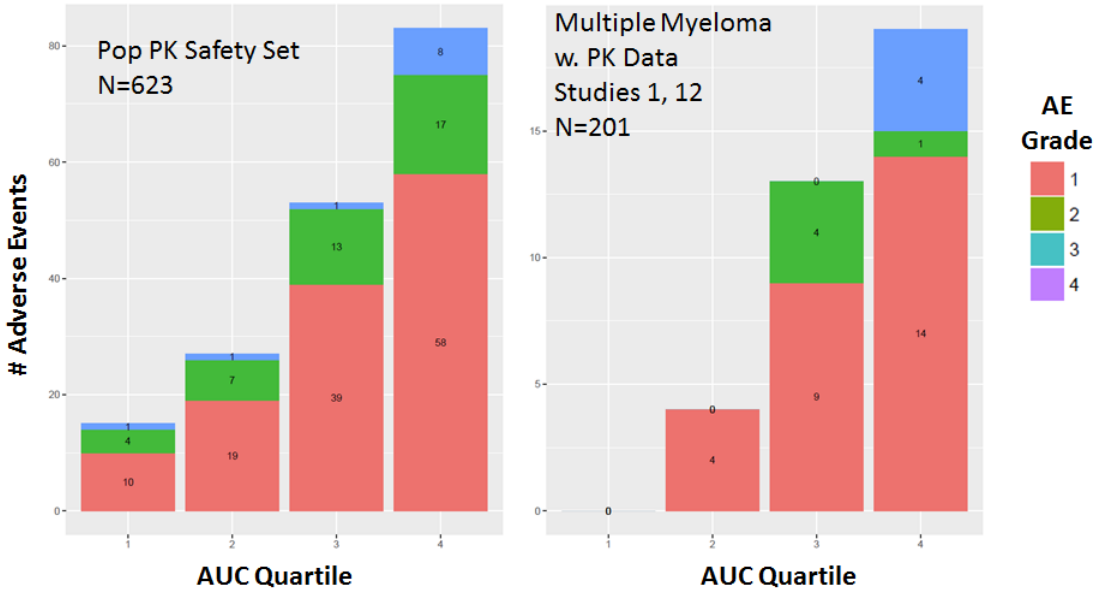
(Source: FDA Analysis)

Figure 15: Exposure-Response Relationship for Gastrointestinal Disorders



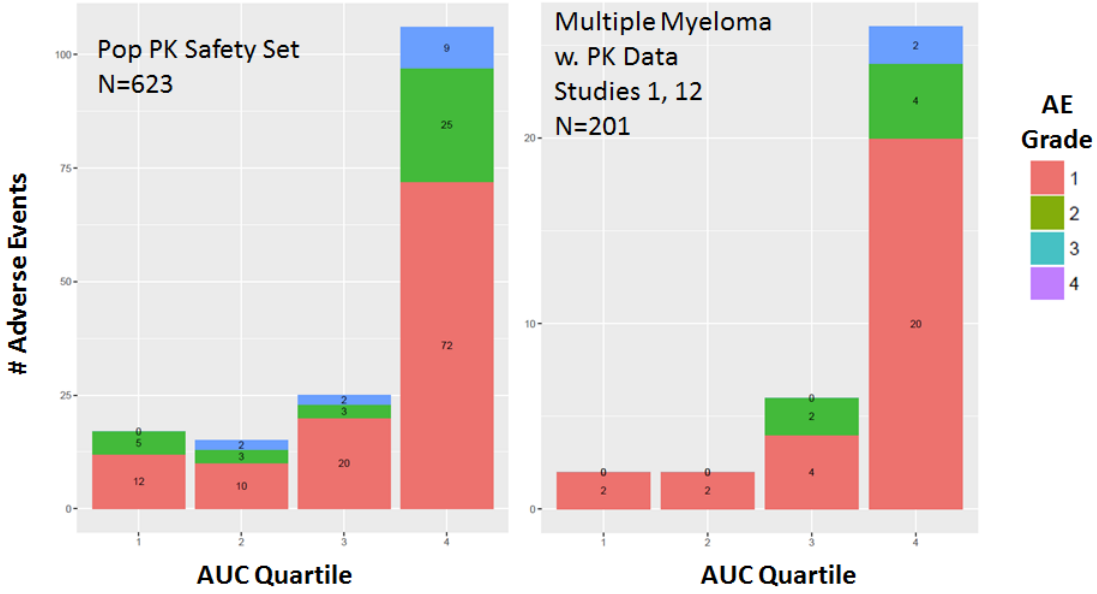
(Source: FDA Analysis)

Figure 16: Exposure-Response Relationship for Diarrhea



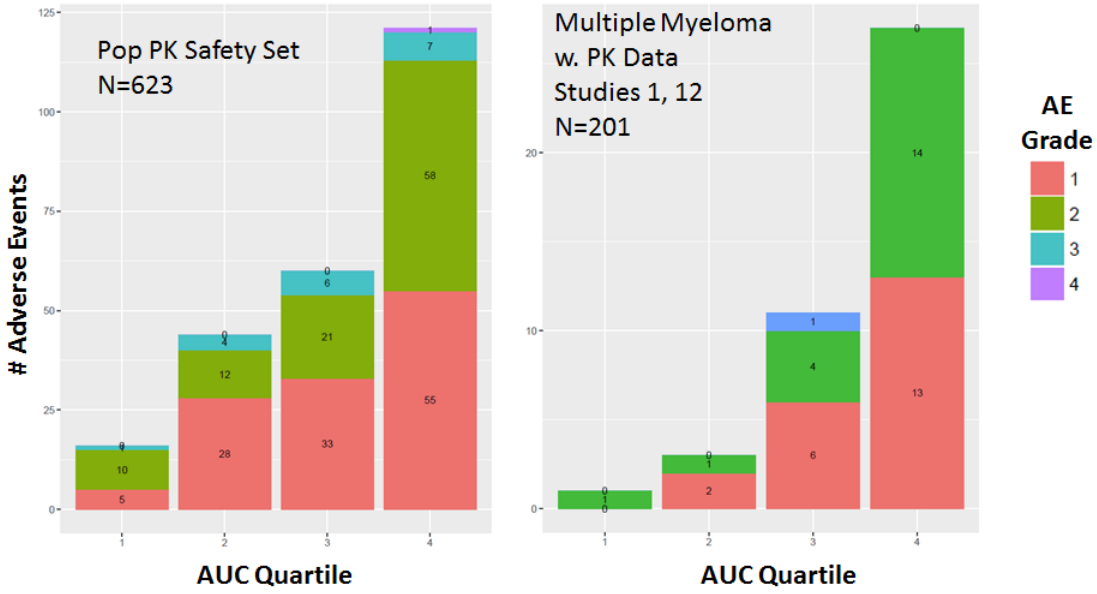
(Source: FDA Analysis)

Figure 17: Exposure-Response Relationship for Vomiting



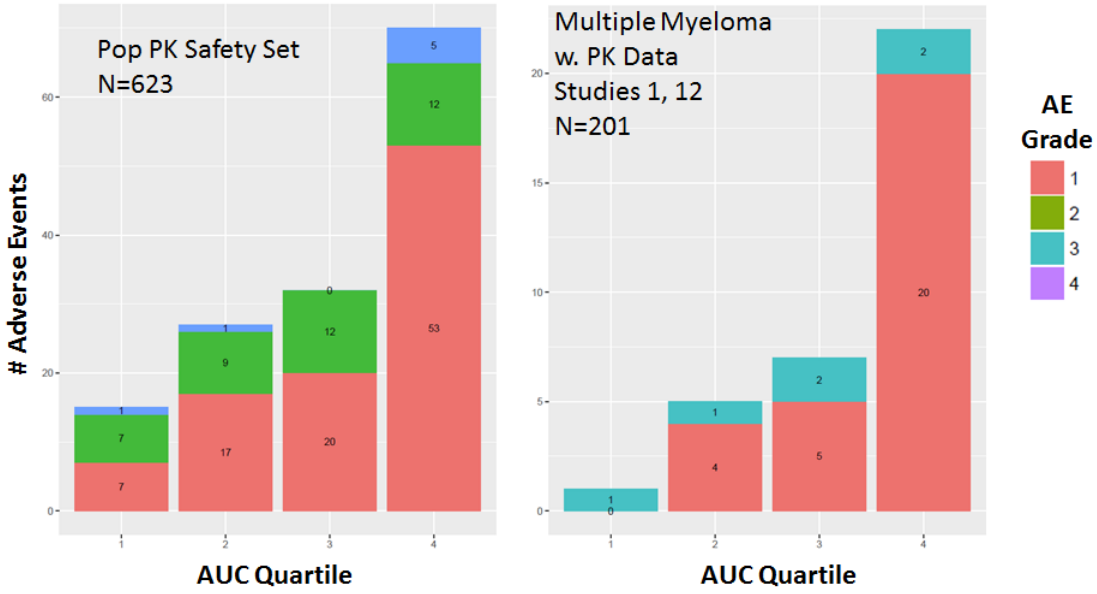
(Source: FDA Analysis)

Figure 18: Exposure-Response Relationship for Decreased Appetite



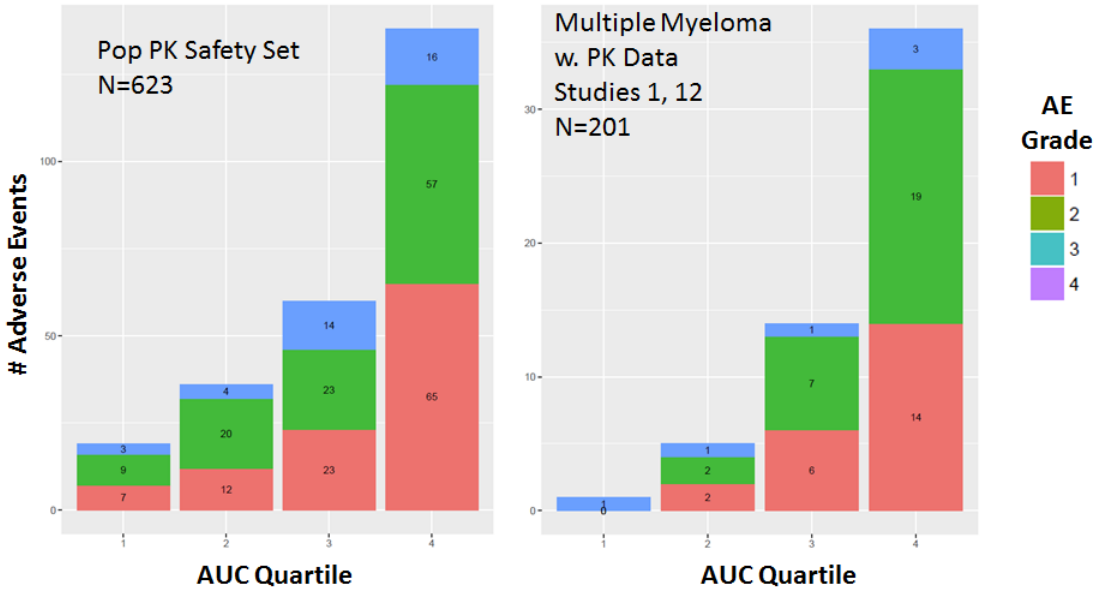
(Source: FDA Analysis)

Figure 19: Exposure-Response Relationship for Decreased Weight



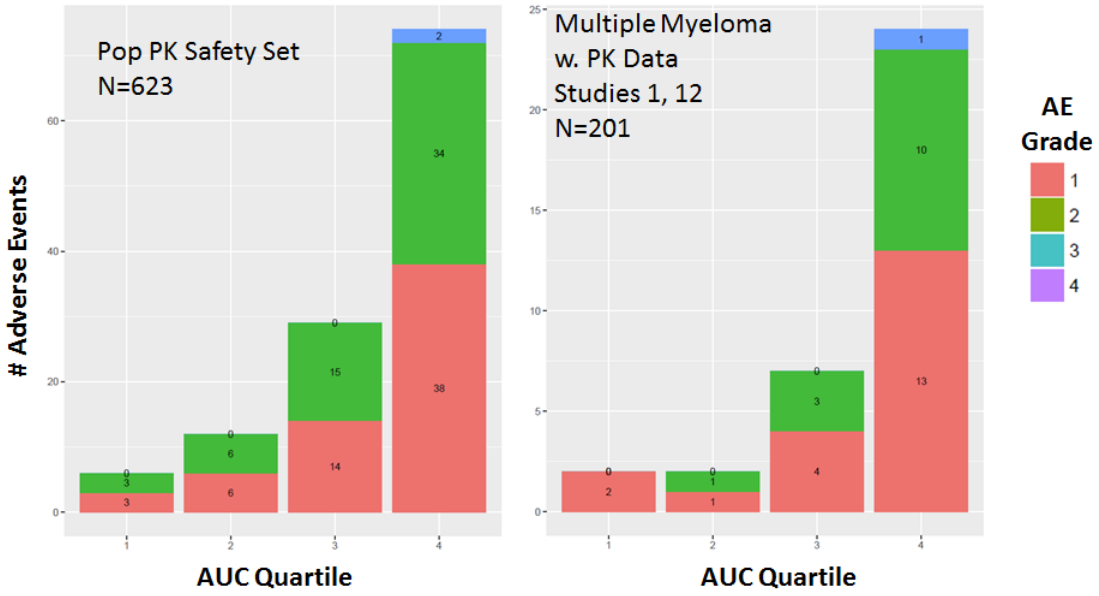
(Source: FDA Analysis)

Figure 20: Exposure-Response Relationship for Fatigue



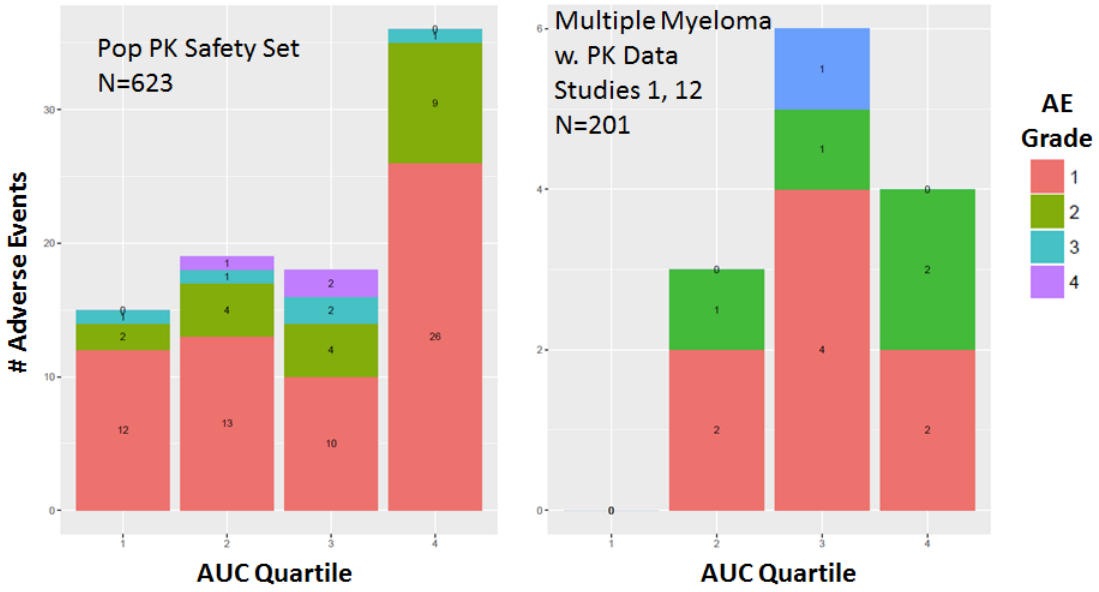
(Source: FDA Analysis)

Figure 21: Exposure-Response Relationship for Hyponatremia



(Source: FDA Analysis)

Figure 22: Exposure-Response Relationship for Ocular Safety Events



(Source: FDA Analysis)