

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212306Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: July 2, 2019
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 212306
Product Name and Strength: Xpovio (selinexor) tablets, 20 mg
Applicant/Sponsor Name: Karyopharm Therapeutics Inc. (Karyopharm)
FDA Received Date: June 17, 2019 and June 28, 2019
OSE RCM #: 2018-1688-3
DMEPA Safety Evaluator: Nicole Garrison, PharmD, BCPS
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised blister pack labels and carton labeling received on June 17, 2019 and June 28, 2019 for Xpovio. We reviewed the revised blister pack labels and carton labeling for Xpovio (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a Additionally, the Applicant submitted a physical sample of the Xpovio 80 mg twice weekly blister pack label and carton labeling.

2 CONCLUSION

After review of the physical sample, we find the contrast between the white font and (b) (4) colored boxing acceptable on the Xpovio 80 mg twice weekly blister pack label and carton labeling. The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Garrison N. Label and Labeling Review for Xpovio (NDA 212306). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUNE 17. RCM No.: 2018-1688-2.

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: June 28, 2019

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Maritsa Serlemitsos-Day, PharmD, BCPS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): XPOVIO (selinexor)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 212306

Applicant: Karyopharm Therapeutics Inc.

1 INTRODUCTION

On August 6, 2018, Karyopharm Therapeutics Inc., submitted for the Agency's review, part 2 of 2 of their rolling submission of an original New Drug Application (NDA) 212306 for the New Molecular Entity (NME) XPOVIO (selinexor) tablets. The proposed indication for XPOVIO (selinexor) tablets in combination with low-dose dexamethasone (Sd), is for the treatment of patients with relapsed refractory multiple myeloma (RRPM) who have received at least 3 prior therapies and whose disease is refractory to at least 1 proteasome inhibitor (PI), at least 1 immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody (mAb).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on September 19, 2018 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for XPOVIO (selinexor) tablets. On March 28, 2019, DHP sent an Information Request to Karyopharm Therapeutics Inc. in which they requested that the Applicant provide a draft Medication Guide (MG) for XPOVIO (selinexor).

2 MATERIAL REVIEWED

- Draft XPOVIO (selinexor) MG received on April 18, 2019 and revised throughout the review cycle and received by DMPP on June 25, 2019.
- Draft XPOVIO (selinexor) Prescribing Information (PI) received on August 6, 2018, revised by the Review Division throughout the review cycle, and received by DMPP on June 25, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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MARITSA SERLEMITOSOS-DAY
06/28/2019 02:11:42 PM

BARBARA A FULLER
06/28/2019 02:18:18 PM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: June 28, 2019

To: Andrea Baines, MD, Clinical Reviewer
Division of Hematology Products (DHP)

Thomas Iype, PharmD, Regulatory Project Manager, DHP

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling, DHP

From: Maritsa Serlemitsos-Day, PharmD, BCPS, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kevin Wright, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for Xpovio™ (selinexor) tablets, for oral use

NDA: 212306

In response to DHP's consult request dated September 19, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for Xpovio™ (selinexor) tablets, for oral use (Xpovio).

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DHP (Suria Yesmin) on June 24, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 17, 2019, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Maritsa Serlemitsos-Day at (301) 796-1760 or maritsa.serlemitsos-day@fda.hhs.gov.

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MARITSA SERLEMITSOS-DAY
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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: June 17, 2019
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 212306
Product Name and Strength: Xpovio (selinexor) tablets, 20 mg
Applicant/Sponsor Name: Karyopharm Therapeutics Inc. (Karyopharm)
FDA Received Date: June 13, 2019
OSE RCM #: 2018-1688-2
DMEPA Safety Evaluator: Nicole Garrison, PharmD, BCPS
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised blister pack labels and carton labeling received on June 13, 2019 for Xpovio. Division of Hematology Products (DHP) requested that we review the revised blister pack labels and carton labeling for Xpovio (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised blister pack labels and carton labeling are unacceptable from a medication error perspective. (b) (4)
readability of the proprietary. Additionally, (b) (4) on labels and labeling for the 160 mg dose (b) (4)

3 RECOMMENDATIONS FOR KARYOPHARM THERAPEUTICS INC.

We recommend the following be implemented prior to approval of this NDA:

^a Garrison N. Label and Labeling Review for Xpovio (NDA 212306). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUNE 07. RCM No.: 2018-1688-1.

A. General Container Labels and Carton Labeling Comments

1. We continue to reiterate that (b) (4) with readability of the proprietary name, (b) (4) We recommend (b) (4) as it may lead to misinterpretation of the proprietary name.
2. For the 160 mg dose, we are concerned (b) (4) may lead to confusion and dispensing errors. Additionally, the end users may misinterpret (b) (4) which could lead to underdosing errors. To provide clarity and mitigate the risk of dispensing and dosing errors, we recommend revising the dose presentation (b) (4) on the blister pack outer labels and carton labeling. For example, revise the (b) (4) to:

80 mg Twice Weekly

Blister Pack

(160 mg total weekly dose)

B. Carton Labeling (Blister Pack Outer Card)

1. See A.2 and revise the blister pack outer card labeling accordingly.
2. We recommend the side display panel of the blister pack outer labeling contain the same information as the primary display panel, i.e. 60 mg once weekly Blister Pack in each respective colored box.

C. Carton Labeling

1. See A.2 and revise the carton labeling accordingly.

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HINA S MEHTA
06/17/2019 09:15:25 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: June 7, 2019
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 212306
Product Name and Strength: Xpovio (selinexor) tablets, 20 mg
Applicant/Sponsor Name: Karyopharm Therapeutics Inc. (Karyopharm)
FDA Received Date: March 13, 2019, April 4, 2019, and April 18, 2019
OSE RCM #: 2018-1688-1
DMEPA Safety Evaluator: Nicole Garrison, PharmD, BCPS
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

This review is in response to revised blister pack labels, carton labels, Prescribing Information, and Medication Guide submitted for Xpovio (Appendix A). Karyopharm submitted a request for a major amendment on March 13, 2019 to NDA 212306 to revise (b) (4)

Our label and labeling recommendations from our previous review were not communicated to the Applicant^a. In the Prescribing Information dated March 13, 2019, we note the Applicant has revised dose modifications for Adverse Reactions and Thrombocytopenia (see below).

(b) (4)

^a Garrison N. Label and Labeling Review for XPOVIO (NDA 212306). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 01. RCM No.: 2018-1688.

Xpovio Dose Modification (b) (4)

Recommended Starting Dose	First Reduction	Second Reduction	Third Reduction	
80 mg Days 1 and 3 of each week (160 mg total per week)	100 mg once weekly	80 mg once weekly	60 mg once weekly	Discontinue

Additionally, in the submission dated March 13, 2019, the Applicant provided revised packaging configurations as follows:

- (b) (4) Each blister pack holds two 80-mg doses. Each dose is comprised of four 20-mg tablets. For prescriptions of 80 mg on Days 1 and 3 of each week.
- (b) (4)
- 100 mg blister packs. Each blister pack holds one 100-mg dose. Each dose is comprised of five 20-mg tablets. For prescriptions of 100 mg once weekly.
- 80 mg blister packs. Each blister pack holds four 20-mg tablets. (b) (4)
(b) (4) prescriptions of 80 mg once weekly.
- 60 mg blister packs. Each blister pack holds one 60-mg dose. Each dose is comprised of three 20-mg tablets. For prescriptions of 60 mg once weekly.

We continue to have concerns about the potential for dispensing errors and dosing errors due to the complexity of the dose reduction schedule and multiple blister packaging options proposed. Specifically, we note that the proposed 80 mg blister pack, which contains four 20-mg tablets, (b) (4)

After internal discussion with DHP, the clinical team decided that they would recommend the standard 80 mg twice weekly dose and the following once weekly dose reductions for both adverse events and thrombocytopenia (to simplify the options):

- 100 once weekly
- 80 mg once weekly
- 60 mg once weekly

Therefore, this alleviated our concerns with the proposed packaging configurations as the standard dosing and dose reductions will align with the blister packaging. We note that (b) (4) will no longer be needed and we recommend removing this option once the Division conveys to the Applicant the proposed, simplified dose reductions.

Additionally, we have identified several areas of improvement with carton labeling and blister pack labels. Table 1 below include the identified medication error issues with the submitted packaging, blister pack labels and carton labeling, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 1: Identified Issues and Recommendations for Karyopharm (*entire table to be conveyed to Applicant*)

General Container Labels and Carton Labeling Comments			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	(b) (4) the proprietary name (b) (4)	(b) (4) readability of the proprietary name, which may lead to misinterpretation of the proprietary name (b) (4)	We recommend (b) (4) as it may lead to misinterpretation of the proprietary name.
2.	The intended storage instructions are not provided to the end- users as an affirmative statement.	End users may not store the product correctly, which may result in product degradation.	Revise the storage temperature from (b) (4) to “Store at or below 30°C (86°F) in all labels and labeling and provide the colored mock ups.
3.	(b) (4) the dose and frequency ((b) (4) 80 mg twice weekly Blister Pack).	Prescribers will likely use the dose and frequency to prescribe Xpovio (e.g., Take 80 mg orally twice weekly). (b) (4) may lead to confusion and dispensing errors. Additionally, the end users may misinterpret (b) (4) which could lead to underdosing errors.	To provide clarity and mitigate the risk of dispensing and dosing errors, we recommend revising the dose presentation on the blister pack outer labels and carton labeling. For example, revise the (b) (4) to: 80 mg Twice Weekly Blister Pack
4.	The Medication Guide Statement is omitted from the principal display panel of the container labels and carton labeling.	The Medication Guide Statement is required for products with Medications Guides per 21 CFR 208.24(d). The Medication Guide statement shall instruct the authorized	Include the statement, “Dispensed enclosed Medication Guide to each patient” on the principal display panel of the container labels and carton labeling.

		dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed and shall state how the Medication Guide is provided.	
Container Labels (Blister Pack Inner Card)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The important warning statements are written using negative statements and are not sufficiently prominent on the Principal Display Panel (PDP).	The important warning statements may easily be overlooked, and negative statements may be misinterpreted as an affirmative action.	Revise the important warning statements as follows: - For the blister packs that administer a dose twice weekly (e.g., 80 mg dose on Day 1 and Day 3), revise the statements, (b) (4) to the following using bold font to increase the prominence: “Take only one dose in a single day. Doses should be administered on Day 1 and Day 3 of each week.” - For the dose packs that administer a dose once weekly (e.g., 60 mg and 100 mg once weekly), remove the following statement as the product is administered once a week and may lead to confusion: (b) (4)
2.	The tablet configuration for the dose packs that will be administered once weekly (e.g., 100	End users may interpret the configuration (b) (4)	For the dose packs that will be administered once weekly (e.g., 100 mg once weekly), place the tablets in one consecutive horizontal row to

	mg once weekly) are presented in two rows.		emphasize that all tablets should be administered at once to achieve the intended dose.
Carton Labeling (Blister Pack Outer Card)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	(b) (4) the dose and frequency ((b) (4) 80 mg twice weekly Blister Pack).	Prescribers will likely use the dose and frequency to prescribe Xpovio (e.g., Take 80 mg orally twice weekly). (b) (4) may lead to confusion and dispensing errors. Additionally, the end users may misinterpret (b) (4) (b) (4) which could lead to underdosing errors.	To provide clarity and mitigate the risk of dispensing and dosing errors, we recommend revising the dose presentation on the blister pack outer labels. For example, revise the (b) (4) (b) (4) statement in the (b) (4) box to: 80 mg Twice Weekly Blister Pack
2.	The Rx Only statement is prominent.	The Rx Only statement appears more prominent than the directions for use on the side panel.	Decrease the prominence by debolding the Rx Only statement.
3.	The product should be swallowed whole; however, there are no cautionary statements on the PDP of the blister pack outer card labeling to inform the intended users.	In Section 2.1 of the Prescribing Information, it states, "Each tablet should be swallowed whole. Patients should not break, chew, crush, or divide the tablets." Thus, this important information should be conveyed on the carton labeling to mitigate the risk of administration errors with Xpovio.	If space permits on the Principal Display Panel (PDP), include the following statement, "Do not cut, crush, or chew the tablets." We recommend this to mitigate the risk of administration errors.
4.	On the back-display panel of the blister card, there are duplicate statements which instruct the users to	Having duplicate statements on the label increases visual clutter.	Remove the duplicate statement, "Swallow (b) (4) whole with water."

	"swallow (b) (4) whole with water."		
5.	The net quantity statement is unclear.	Lack of clarity of the net quantity may result in administration errors.	Revise the net quantity statements on the Principal Display panel as follows (e.g.): Blister pack contains 8 tablets (20 mg per tablet)
6.	The (b) (4) colored box used in the presentation of the proprietary name competes in prominence with the colored boxing used to differentiate the doses on the blister pack labels.	Inadequate use of color between the different dose presentations may lead to dispensing and subsequent dosing errors.	We recommend you increase the amount of color (e.g., (b) (4) for the 80 mg twice weekly dose) used to differentiate the different dose presentations. You may also consider removing or reducing the amount of the (b) (4) colored box.
7.	There is a (b) (4) the unit of measure (mg), below the proprietary and established name, and net quantity statement on the principal display panel.	The (b) (4) on principal display panel decreases visibility of important information.	We recommend removing the (b) (4) on the principal display to increase visibility of important information.

Carton Labeling

1.	The (b) (4) background color competes in prominence with the colored boxing used to differentiate the doses on the carton labeling.	Inadequate use of color between the different dose presentations may lead to dispensing and subsequent dosing errors.	We recommend you increase the amount of color (e.g., (b) (4) for the 80 mg twice weekly dose) used to differentiate the different dose presentations. You may also consider removing or reducing the amount of the (b) (4) colored background on the carton labeling.
2.	(b) (4)	Prescribers will likely use the dose and frequency to	To provide clarity and mitigate the risk of dispensing

	(b) (4) the dose and frequency ((b) (4) 80 mg twice weekly Blister Pack).	prescribe Xpovio (e.g., Take 80 mg orally twice weekly). (b) (4) may lead to confusion and dispensing errors. Additionally, the end users may misinterpret (b) (4) which could lead to underdosing errors.	and dosing errors, we recommend revising the dose presentation on the carton labeling. For example, revise the (b) (4) statement in the (b) (4) box to: 80 mg Twice Weekly Blister Pack
3.	The net quantity statement is unclear.	Lack of clarity of the net quantity may result in administration errors.	Revise the net quantity statements on the Principal Display Panel as follows (e.g.): Contents: 4 individual weekly blister packs. Each blister pack contains 8 tablets (20 mg per tablet) 32 Film-coated tablets
4.	(b) (4) (National Drug Code) NDC on the carton and container labels.	(b) (4) NDC package code (last 2 digits of the NDC) (b) (4)	(b) (4) Revise all the NDC numbers (b) (4)
5.	The Rx Only statement is prominent.	The Rx Only statement appears more prominent than the directions for use on the side panel.	Decrease the prominence by debolding the Rx Only statement
6.	The area for the lot number and expiration	The lot number statement is required on the	Revise the carton labeling to include the lot number and

	date are omitted from the outer carton labeling.	immediate container and carton labeling when there is sufficient space per 21 CFR 201.10(i)(1). The expiration date is required on the immediate container and carton labeling per 21 CFR 201.17.	expiration date in accordance with 21 CFR 201.10(i)(1) and 21 CFR 201.17.
Packaging			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The proposed 80 mg blister pack, which contains four 20-mg tablets, (b) (4)	We are concerned that (b) (4) may be confusing and lead to wrong dose errors.	We recommend developing a separate dose pack for the 80 mg once weekly dose.

2 CONCLUSION

The Applicant submitted revised blister pack labels, carton labels, Prescribing Information, and Medication Guide received on March 13, 2019, April 4, 2019, and April 18, 2019 for Xpovio. Our evaluation of the Medication Guide was acceptable from a medication error perspective. Our evaluation of the proposed blister pack labels and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 1 for the Applicant. We ask that the Division convey Table 1 in its entirety to the Kayopharm so that recommendations are implemented prior to approval of this NDA 212306.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 1, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 212306
Product Name and Strength:	Xpovio (selinexor) tablets, 20 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Karyopharm Therapeutics Inc. (Karyopharm)
FDA Received Date:	June 29, 2018, August 6, 2018, September 10, 2018, and December 27, 2018
OSE RCM #:	2018-1688
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF REVIEW VS REASON FOR REVIEW

As part of the approval process for NDA 212306 Xpovio (selinexor) tablets, 20 mg, the Division of Hematology Products (DHP) requested that we review the proposed blister pack labels, blister pack labeling, Prescribing Information (PI), and Patient Information for areas that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C- N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E- N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

We note the recommended starting dose is 80 mg orally on days 1 and 3 of each week with dosage reductions for adverse reactions. Karyopharm proposes (b) (4) dosage reductions (see below).

(b) (4)

With respect to packaging, Xpovio will be available as 20 mg tablets, packaged in blister packs as follows:

[REDACTED] (b) (4)

We are concerned about the potential for dosing errors with the complex dose reduction schedule and multiple options available. We note that the proposed blister packaging options do not align with all of the potential dose reductions as proposed by the applicant. For example, [REDACTED] (b) (4)

[REDACTED]

After internal discussions with the clinical and clinical pharmacology reviewers, an information request (IR) was sent to Karyopharm on December 19, 2018, [REDACTED] (b) (4). Furthermore, the IR outlined concerns about the proposed dose modifications of 'once weekly' due to a potentially higher C_{max} (relative to the patient's previous dose) and also asked the applicant to discuss their plans to mitigate the risk of medication errors associated with [REDACTED] (b) (4).

[REDACTED]

On December 28, 2018, Karyopharm responded with a proposal [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

Excerpted from December 28, 2018 Information Request Response.

Excerpted from December 28, 2018 Information Request Response.

In addition, Karyopharm proposed to modify the blister packs to 20 mg per tablet in blister packs as follows:

- 60 mg once a week dosing (contains one dose)
- 80 mg once a week dosing (b) (4)
- 100 mg once a week dosing (contains one dose)
- (b) (4)
- 160 mg pack containing 80 mg dose on day 1 and 80 mg dose on day 3 of each week (starting dose).

We defer to the clinical team for the determination of the appropriate dose reductions. However, based on preliminary discussions, it appears that the division will approve an 80 mg once weekly, 80 mg twice weekly, and 100 mg once weekly dosing and packaging configurations. Thus, the proposed packaging configurations will align with the potential dose reductions. Additionally, we have identified several concerns with carton labeling and blister pack labels.

Tables 2 and 3 below include the identified medication error issues with the submitted packaging, blister pack labels, carton labeling, and Prescribing Information, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Hematology Products

Prescribing Information			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information			
1.	In Section 2.1 Recommended Dosage, (b) (4); however, the Patient Information, blister pack labels and labeling advise	There is incongruency between the labels and labeling (b) (4) for administration of Xpovio.	Revise the statement in Section 2.1 Recommended Dosage of the Prescribing Information to "Each tablet should be swallowed whole with water." for consistency with the Patient Information,

	users to take Xpovio with water.		blister pack labels and labeling. Delete the statement, (b) (4)
2.	The dose modification schedule for adverse reactions in Table 1 (b) (4)	(b) (4) makes the regimen more complex and prone to administration errors.	We recommend simplifying (b) (4) which may decrease the risk of administration errors.
3.	In Section 16 How Supplied, the intended storage instructions are not provided.	End users may not store the product correctly, which may result in product degradation.	Revise the storage temperature (b) (4)
4.	In Section 16 How Supplied, (b) (4) (National Drug Code) NDC on the carton and container labels.	(b) (4) NDC package code (last 2 digits of the NDC) (b) (4)	(b) (4) Revise all the NDC numbers (b) (4)

Table 3: Identified Issues and Recommendations for Karyopharm (*entire table to be conveyed to Applicant*)

General Container Labels and Carton Labeling Comments			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	(b) (4) the proprietary name (b) (4)	(b) (4) the proprietary name competes with readability of the proprietary name, (b) (4)	(b) (4) in the proprietary name as it may lead to misinterpretation of the proprietary name.
2.	The intended storage instructions are not provided to the end-users as an affirmative statement.	End users may not store the product correctly, which may result in product degradation.	Revise the storage temperature from (b) (4) in all labels and provide the colored mock ups.
Container Labels (Blister Pack Inner Card)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The dose of the full package (b) (4)	End users may misinterpret (b) (4) which could lead to underdose errors.	To provide clarity and mitigate dosing errors, we recommend revising the (b) (4) on the inner card of the blister labels. (b) (4) In addition, add

			“Take 4 tablets as a single-dose. Swallow whole with water.”
2.	The important warning statements are not prominent on the Principal Display Panel (PDP) and is written using negative statements.	The important warning statements may easily be overlooked, and negative statements may be misinterpreted as an affirmative action.	Revise the important warning statements as follows: • Increase the prominence of the important warning statements as they may be easily overlooked due to inadequate contrast with the shiny metal foil on the PDP of the inner card of the blister pack. • For the dose pack administer twice weekly (e.g. 80 mg dose on Day 1 and Day 3), revise the statements in bold font, (b) (4) [REDACTED] to “Take only one dose in a single day. Doses should be administered on Day 1 and Day 3 of each week.” • For the dose packs that will be administered once weekly (e.g. 80 mg once weekly and 100 mg once weekly), delete the statement, (b) (4) [REDACTED] as the product will only be administered once weekly for dose reductions. • For the dose packs that will be administered once weekly (e.g. 80 mg once weekly and 100 mg once weekly), align the tablet

			configuration in one consecutive horizontal row (instead of two rows) as this will further emphasize that all tablets should be administered at one time to achieve the intended dose.
Carton Labeling (Blister Pack Outer Card)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The dose of the full package (b) (4)	End users may misinterpret (b) (4) which could lead to underdose errors.	To provide clarity and mitigate underdose errors, we recommend revising (b) (4) on the carton labeling. • Revise the dose (e.g., 80 mg) in the (b) (4) color box to read as: (b) (4)
2.	The Rx Only statement is prominent.	The Rx Only statement appears more prominent than the directions for use on the side panel.	Decrease the prominence by debolding the Rx Only statement.
3.	The product should be swallowed whole; however, there are no cautionary statements on the PDP of the blister pack outer card labeling to inform the intended users.	In Section 2.1 of the Prescribing Information, it states, “Each tablet should be swallowed whole. Patients should not break, chew, crush, or divide the tablets.” Thus, this important information should be conveyed on the carton labeling to mitigate the risk of administration errors with Xpovio.	If space permits on the Principal Display Panel (PDP), include the following statement, “Do not cut, crush, or chew the tablets.” We recommend this to mitigate the risk of administration errors.
4.	On the back-display panel of the blister card, there are duplicate statements which	Having duplicate statements on the label increases visual clutter.	Remove the duplicate statement, “Swallow (b) (4) whole with water.”

	instruct the users to “swallow (b) (4) whole with water.”		
5.	The net quantity statement is unclear.	Lack of clarity of the net quantity may result in administration errors.	Revise the net quantity statements on the Principal Display panel as follows (e.g.): Each blister pack contains 8 tablets (20 mg per tablet) 8 Film-coated tablets
Carton labeling			
1.	The dose of the full package (b) (4)	End users may misinterpret (b) (4) which could lead to underdose errors.	To provide clarity and mitigate underdose errors, we recommend revising the (b) (4) on the carton labeling. • Revise the dose (e.g., 80 mg) in the (b) (4) color box to read as: (b) (4)
2.	The net quantity statement is unclear.	Lack of clarity of the net quantity may result in administration errors.	Revise the net quantity statements on the Principal Display Panel as follows (e.g.): Contents: 4 individual weekly blister packs. Each blister pack contains 8 tablets (20 mg per tablet) 32 Film-coated tablets
3.	(b) (4) (National Drug Code) NDC on the carton and container labels.	(b) (4) NDC package code (last 2 digits of the NDC)	(b) (4)

		(b) (4)	(b) (4) Revise all the NDC numbers (b) (4)
4.	The Rx Only statement is prominent.	The Rx Only statement appears more prominent than the directions for use on the side panel.	Decrease the prominence by debolding the Rx Only statement
5.	The area for the lot number and expiration date are omitted from the outer carton labeling.	The lot number statement is required on the immediate container and carton labeling when there is sufficient space per 21 CFR 201.10(i)(1). The expiration date is required on the immediate container and carton labeling per 21 CFR 201.17.	Revise the carton labeling to include the lot number and expiration date in accordance with 21 CFR 201.10(i)(1) and 21 CFR 201.17.
Packaging			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The proposed packaging is a fixed blister package with a 60 mg weekly dose, 80 mg weekly dose (b) (4) 100 mg weekly dose, (b) (4) dose, and (b) (4) dose.	The starting dose for Xpovio is 80 mg given twice weekly (b) (4) Xpovio may be dose reduced to 80 mg administered once weekly packaged in an 80 mg blister pack. We are concerned that (b) (4) In addition, two blister packs contain an 80 mg dose, however the frequency of administration differs (once	We recommend the dose pack be labeled as the total daily dose (80 mg) (b) (4) Please consider ways to differentiate the frequency of administrations for the 80 mg dose (once vs. twice weekly) through the use of different colors, boxing, or some other means.

		vs. twice weekly) and may result in wrong dose errors.	
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4 CONCLUSION

Our evaluation of the proposed Prescribing Information, Patient labeling, blister pack labels and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to the Kayopharm so that recommendations are implemented prior to approval of this NDA 212306.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Xpovio that Karyopharm submitted on June 29, 2018 and September 10, 2018.

Table 4. Relevant Product Information for Xpovio	
Initial Approval Date	N/A
Active Ingredient	Selinexor
Indication	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).
Route of Administration	Oral
Dosage Form	Tablets
Strength	20 mg
Dose and Frequency	The recommended starting dose of Xpovio is 80 mg; taken orally on days 1 and 3 of each week. Xpovio Dose Modifications for Adverse Reactions
How Supplied	

	(b) (4)
Storage	(b) (4)
Container Closure	(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On November 1 ,2018, we searched the L:drive and AIMS using the terms, Xpovio to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any previous labeling reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Xpovio labels and labeling submitted by Karyopharm on June 29, 2018, September 10, 2018, and December 27, 2018.

- Blister pack labels received on June 29, 2018 and December 27, 2018
- Blister pack labeling received on June 29, 2018 and December 27, 2018
- Patient Information received on September 10, 2018
- Prescribing Information (Image not shown) received on September 10, 2018

F.2 Label and Labeling Images

Blister pack labels

60 mg Dose



^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

NICOLE B GARRISON
03/01/2019 04:13:19 PM

HINA S MEHTA
03/01/2019 04:48:23 PM

Medical Officer's Review of NDA 212306
Ophthalmology Consult

NDA 212306
Consult Review

Submission Date August 6, 2018
Consult Request: October 2, 2018
Review completed: January 28, 2018

Product Name: Selinexor

Sponsor: Karyopharm Therapeutics Inc.

Requested: Please review safety data and patient narratives for ocular adverse events and comment on any concerns, recommended monitoring/mitigation strategies, recommended management guidelines, and any other implications for labeling.

Submitted: Ocular Safety Review. Patients (N=1458) from all CSTs including selinexor alone or in four different trials that had combination therapies including three that included dexamethasone. Patients in these studies had relapsed and/or refractory cancers and most were treated with multiple lines of anti-cancer therapy prior to study entry. Selinexor doses were divided into low (<120 mg/week), medium (120-160 mg/week), and high (>160 mg/week) doses.

In these safety population, eye disorder events were found in 431 (30%) patients (ocular AE patient population). Of these 431 patients, 86.8% were white, non-Hispanic and 5.3% were black or African American, which is similar to the entire safety population with 84.8% white non-Hispanic and 6.4% black or African American. No other racial group had greater than a 3% incidence of eye disorder events. These demographic data indicate that there is no racial group at a unique risk for ocular AE susceptibility. The most complete information appears to be that from the screening examination and from the final exam with much less complete information at unscheduled visits. With few exceptions these unscheduled visits do not appear to be for ophthalmic complaints. There is a minimal amount of missing data. A change of less than two lines on the Snellen visual acuity was considered insignificant. The other visual acuity change that was considered important was the progression to 20/60 or worse, the range in which cataract surgery is often needed. The median age of the safety study population is 65.0 years and for the ocular AE group is 63.0 years at the time of screening. Thirteen (3.0%, 13/431) of the patients in the ocular AE population are more than 80 years old.

AE	(N= 431) (%)
Cataract	50 (12%)
Vision Blurred	249 (58%)

Reviewer's Comment: *The clinical development program has demonstrated that Selinexor in combination with dexamethasone increases the incidence of cataract development. However, since dexamethasone is known to increase the incidence of cataract development, it is not possible to separate the contribution of Selinexor versus the contribution of dexamethasone to the development of cataracts.*

Cataract development leads to blurred vision even before the cataract is identified by slit lamp examination. Therefore it is not possible to separate blurred vision from cataract development.

It is recommended that the labeling clearly identify the potential of Selinexor in combination with dexamethasone to increase the development of cataracts.

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

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/s/

WILEY A CHAMBERS
01/29/2019 06:30:20 PM

Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA 212306
Submission Number	003
Submission Date	08/06/2018
Date Consult Received	09/19/2018
Clinical Division	DHP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult regarding the sponsor's QT evaluation. The QT-IRT reviewed the following materials:

- Previous QT-IRT review under IND 114042 dated 06/06/2018 in DARRTS;
- Study [kcp-330-001](#) protocol and study report (Submission 0003);
- Study [kcp-330-003](#) protocol and study report (Submission 0003);
- [Concentration-QTc analysis report](#) (Submission 0003); and
- [Highlights of clinical pharmacology and cardiac safety](#) (Submission 0012)
- Response to IR Letter (dated [12/20/2018](#)).

1 SUMMARY

No large QTc prolongation effect (i.e., >20 ms) of selinexor was observed in this QT assessment. The effect of selinexor was evaluated in Studies KCP-330-001 and KCP-330-003. The highest dose evaluated in the two studies was 80 mg/m², which covers the therapeutic exposure (80 mg taken weekly on Day 1 and 3). The worse-case exposure scenario due to drug-drug interaction or organ impairment has not been determined. The data from the two studies was analyzed by using exposure-response analysis as the primary analysis, which did not suggest that selinexor is associated with large mean increases in the QTc interval (refer to section 4.5) – see Table 1 for overall results.

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG parameter	Treatment	Concentration	Δ (ms)	90% CI (ms)
QTcF	80 mg	680 ng/mL	4.4	(1.0, 7.8)

There was a total of 13/196 (6.6%) patients with QTc >500 or change from baseline QTc >60 ms. Two patients [2/196 (1%)] with post-treatment QTcF >=500 ms also had QTc >60 ms change from baseline. These patients had concomitant QT prolonging medications and electrolyte abnormalities (particularly hypokalemia, hypomagnesemia, or hypocalcemia) that may have contributed to their QTc prolongation. In addition, QTc prolongation was reported as an AE in 28 patients — 2 patients had grade 3 QT prolonged AEs; all others were grade 1 or 2, none of them were serious AEs. Without a control arm or a thorough characterization of selinexor's effect on cardiac repolarization, it is difficult to know whether these cases of QTc prolongation in the clinical trials are related to selinexor exposure or represent background events in the patient population.

Selinexor inhibits hERG channel (IKr) with an IC50 value of 20.6 µM. The IC50 value, based on human plasma protein binding of 95.1% and mean Cmax of 1.53 µM, is estimated to be ~250X higher than the free unbound Cmax of 0.07 µM following an 80 mg dose.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 PROPOSED LABEL

Below are proposed edits to the label submitted to [SDN 003](#) from the QT-IRT. Our changes are highlighted ([addition](#), ~~deletion~~). Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of multiple doses of TRADENAME up to 175 mg twice weekly on the QTc interval was evaluated in patients with heavily pretreated hematologic malignancies. TRADENAME had no [large](#) effect ([i.e. 20 ms](#)) on QTc interval [at the therapeutic dose level](#) (b) (4)

[6.6% patients had QTc >500 or change from baseline QTc >60 ms.](#)

Reviewer's comment:

The studies used to support the QT assessment does not have a placebo arm or positive control arm. Per ICH E14 Q&A 6.1, the assessment can be used to support a lack of large mean effect (i.e. 20 ms) on QTc interval, but it cannot be used to exclude a small mean effect (i.e. 10 ms). The exposure-response analysis is limited by ECG acquisition (e.g. paper ECG without replicate measurements). In addition, sponsor's and reviewer's analysis suggested a trend of positive relationship between Δ QTcF and selinexor. Therefore, we propose to remove the statement of (b) (4)

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

The QT-IRT reviewed a QT assessment proposal previously under IND 114042 (DARRTS 06/06/2018). Sponsor did not provide sufficient information to support an evaluation of the QT assessment proposal.

In the current submission, the sponsor submitted a concentration-QTc analysis using data from Studies KCP-330-001 and KCP-330-003. Table 2 provides a summary of study population, dose, and time-matched PK/ECG data. Paper ECGs were collected as a safety endpoint in these studies and were assessed using the device algorithm. The planned number of ECGs per time-point was at least one with the option to collect more as

medically indicated (IR response dated [11/14/2018](#) submitted to sequence 0030). Sponsor did not conduct central tendency analysis or categorical analysis.

Table 2. Summary of Studies Included in the Combined Dataset

Study	Phase	Dose Range (mg)	Subjects (n†)	Study Description	Time-matched Sampling Post-Dose* (hrs)
KCP-330-001	I	4-160	79	Advanced hematological malignancies	1, 2, 4, 8, 24, 48
KCP-330-003	Ib	60	6	Soft-tissue or bone sarcoma	0.5, 1.5, 2, 3, 4, 5

† Number of subjects who have valid time-matched Δ QTc and PK measurements; * All time-matched data were collected post-dose in cycle 1, with the exception of one value at 24 hrs post-dose in cycle 2

Source: Table 1 in [Concentration-QTc analysis report](#)

Study KCP-330-001 is a Phase 1 study, dose escalation study of selinexor in patients with advanced hematological malignancies. It contains 8 treatment arms and 11 dose schedules. In Cycle 1, ECG data were collected at predose and 2 and 4 hr postdose on C1D1 in all schedules, and at predose on C1D2 and/or C1D3 in some schedules. Sponsor has submitted ECG data for 174 subjects in Study KCP-330-001 and 21 patients in Study KCP-330-003. Because Study KCP-330-001 has adequate number of subjects on selinexor monotherapy and receiving a dose higher than the proposed therapeutic dose level, this study is used as primary source of data in reviewer's analysis. A description of individual dataset that was used to support reviewer's analysis was include in the corresponding sections.

3.2 SPONSOR'S RESULTS

3.2.1 Central tendency analysis

The sponsor used exposure-response analysis for their primary assessment based on data from Studies KCP-330-001 and KCP-330-003. The statistical reviewer conducted central tendency analysis based on selected data from Study KCP-330-001. Conclusions from the reviewer's central tendency analysis are consistent with that of exposure-response analysis from the sponsor, i.e., no large QT prolongation effect (>20 ms) was found for selinexor in the study. Please see section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

Not Applicable

3.2.1.1.1 QT bias assessment

Not applicable.

3.2.2 Categorical Analysis

Based on the reported ECG values, all the outliers were from Study KCP-330-001 (Study 001), none from study KCP-330-003 (Study 003).

Table 3. Categorical Outlier Analysis (Response to IR 12/20/2018)

Category	Study KCP-330-001			Study KCP-330-003			Total (N=196; %)*
	Low (< 30 mg/m ²) (N=45; %)	Medium (≥30 mg/m ² and <55 mg/m ²) (N=74; %)	High (≥55 mg/m ²) (N=56; %)	30 mg/m ² (N=9)	50 mg/m ² (N=6)	60 mg flat (N=6)	
QTcF>500 ms	3 (6.7)	2 (2.7)	2 (3.6)	0	0	0	7 (3.6)
QTcF>500 ms and change from baseline>60 ms	1 (2.2)	1 (1.4)	0	0	0	0	2 (1.0)
QTcF>480 ms and ≤500 ms	3 (6.7)	7 (9.5)	4 (7.1)	0	0	0	14 (7.1)
QTcF>480 ms and ≤500 ms and change from baseline>60 ms	2 (4.4)	2 (2.7)	1 (1.8)	0	0	0	5 (2.6)
QTcF Change from baseline>60 ms	2 (4.4)	4 (5.4)	2 (3.6)	0	0	0	8 (4.1)
PR interval ≥220 ms	2 (4.4)	3 (4.1)	2 (3.6)	0	0	0	7 (3.6)
PR interval ≥220 ms and 25% increase from baseline	0	0	0	0	0	0	0
QRS interval ≥110 ms	10 (22.2)	5 (6.8)	6 (10.7)	0	0	0	21 (10.7)
QRS interval ≥110 ms and 25% increase from baseline	0	1 (1.4)	1 (1.8)	0	0	0	2 (1.0)

*Note: Since not every patient in safety population have ECG measurement collected, the N in the table are smaller than the corresponding safety population. ECG data included were from the start date of selinexor treatment until 30 days post selinexor treatment.

The sponsor provided narrative summaries for electrocardiogram results (section 3.2.3).

The statistical reviewer conducted categorical analysis based on available data from arms in which selinexor was administrated as monotherapy, which might cause small discrepancies between the sponsor's results and the reviewer's results. No outliers for the ECG measurements except HR came from study 003 in the reviewer's analysis. Please see section 4.4 for additional details.

3.2.3 Safety Analysis

In Study KCP-330-001, which included patients with a variety of advanced, heavily pretreated hematologic malignancies, there was no particular malignancy associated with being an ECG outlier. Outliers occurred across all dose levels, and there was no association with dose, which is aligned with the conclusion from our concentration-QT analysis (only a weak positive concentration-QTc relationship identified).

There was a total of 13 patients with QTc >500 or change from baseline QTc >60 ms. Two patients with post-treatment QTcF ≥500 ms also had QTc >60 ms change from baseline. Their concomitant medications that may prolong QT, the electrolyte abnormalities (particularly hypokalemia, hypomagnesemia, hypocalcemia) and maximum QTcF value are listed in the table below.

There were no cases of Torsade de Pointes or other ventricular arrhythmia associated with the ECG findings.

Table 4. Summary of Patients with QTcF >500 ms or QTcF >60 ms change from baseline (Response to IR 12/20/2018)

	Patient Identifier	Malignancy	Baseline QTcF (ms)	QTcF Outlier (ms)	Potential Concomitant QTc Prolonging Medications	Calcium Value (mmol/L)	Magnesium Value (mmol/L)	Potassium Value (mmol/L)
1	(b) (6)	Non-Hodgkin's Lymphoma	485.9	516.8	hydroxyzine	2.2	0.7	5.0
2		Multiple Myeloma	357.3	458.9	quetiapine, sulfamethoxazole-trimethoprim	1.7*	0.5*	3.9
3		Multiple Myeloma	483.1	536.8	sulfamethoxazole-trimethoprim, omeprazole	1.8*	0.9	5.3†
4		Chronic Lymphocytic Leukemia	509.0	536.0	citalopram, furosemide, fluconazole, olanzapine, azithromycin	2.3	1.2†	5.7†
5		Acute Lymphoblastic Leukemia	415.6	492.3	ondansetron, pentamidine, diphenhydramine, dextromethorphan	2.1*	0.7	3.8
6		Non-Hodgkin's Lymphoma	404.7	485.2	diphenhydramine, ondansetron	2.1*	0.9	3.9
7		Chronic Lymphocytic Leukemia	475.7	507.4	amiodarone, mirtazapine, ondansetron	2.5	0.7	4.1
8		Acute Myeloid Leukemia	373.2	465.9	esomeprazole, tramadol, voriconazole, loperamide, mirtazapine	—	—	3.7
9		Multiple Myeloma	512.9	517.2	loperamide, mirtazapine, ondansetron, esomeprazole	1.8*	0.7	3.5
10		Waldenstrom's Macroglobulinemia	403.2	511.6	diphenhydramine, propofol, esomeprazole, levofloxacin, ondansetron, olanzapine	2.2	0.7	3.9
11		Acute Myeloid Leukemia	418.1	497.8	palonosetron, olanzapine, promethazine, metoclopramide	2.1*	0.7	4.2
12		Acute Myeloid Leukemia	414.6	502.1	fluconazole, diphenhydramine, ondansetron, olanzapine	2.2	0.5*	4.1
13		Acute Myeloid Leukemia	414.2	481.2	fluconazole, citalopram	2.3	0.7*	3.7

Note: the electrolyte values were collected within the period of 5 days prior (inclusive) and 5 days post (inclusive) the QTcF outlier

There were 21 patients (of 28, 75%) from Study KCP-330-001 and 7 patients from Study KCP-330-003 with reported AE of electrocardiogram (ECG) QT prolonged. Two subjects reported a Grade 3 QT prolongation; the other AEs were Grade 1 [12 subjects] or Grade 2 [14 subjects]. Several of the patients with reported AEs of ECG QT prolonged did not have corresponding QT values reported.

Reviewer's comment: Patients with large increases in QTc had concomitant QT prolonging medications or electrolyte imbalances that could have contributed to their QTc prolongation.

None of the adverse events identified to be of clinical importance per the ICH E14 guidelines (i.e., syncope, significant ventricular arrhythmias or sudden cardiac death) occurred in these studies. Patient (b) (6) reported a SAE of seizure grade 2, but this event was not associated with a cardiac event. A CT scan of the head showed new bilateral subfrontal and left-temporal acute hematomas on chronic subdural hematomas, which were cited as the cause of the seizures.

3.2.4 Exposure-Response Analysis

Sponsor used the NONMEM software to develop a population concentration-QTc model assuming a direct effect, linear relationship. No covariates (age, weight, height, body surface area, and baseline QTcF) were identified as statistically significant. The final model was $\Delta\text{QTcF} \sim \text{CONC}$ with a between-subject-variability placed on slope. The upper bound of the two-sided 90% CI for predicted ΔQTcF was expected to exceed 20 ms at a concentration of 1523 ng/mL, which was approximately 3-fold higher than the C_{max} at the recommended therapeutic dose of 80 mg.

The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.5 for additional details.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no significant increases or decreases in heart rate (i.e. mean < 10 bpm) were observed (see Sections 4.3.2 and 4.5).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Paper ECGs were submitted.

4.2.2 QT bias assessment

Not conducted.

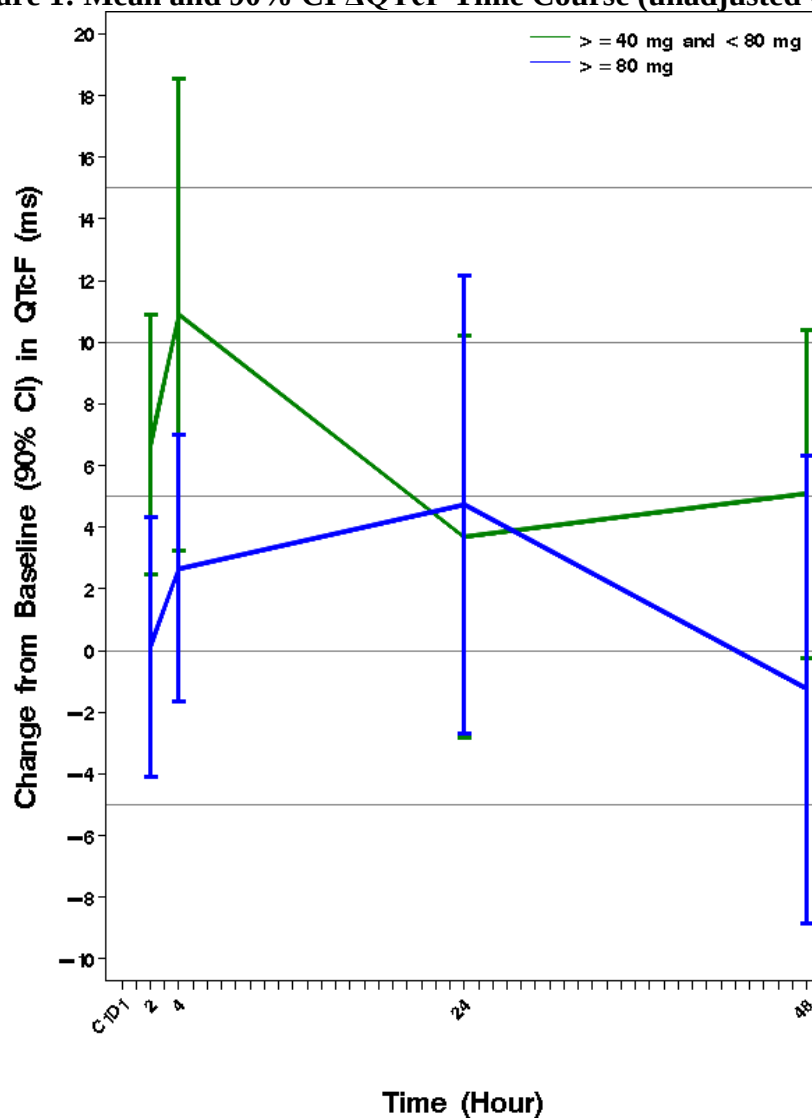
4.3 CENTRAL TENDENCY ANALYSIS

4.3.1 QTc

Selected Cycle 1 Day 1 data up to 48 hours (Arm 1 Schedule 3; Arm 2 Schedules 3, 8, and 10; Arm 3, 4, and 5) from Study KCP-330-001 were used for central tendency analysis. The statistical reviewer analyzed the Δ QTcF effect using summary statistics.

The following figure displays the time profile of Δ QTcF of different dose groups for the selected data. The largest upper limits of 90% CI for the mean change from baseline in QTcF (Δ QTcF) were less than 20 ms for both ≥ 40 mg and < 80 mg group and ≥ 80 mg group.

Figure 1: Mean and 90% CI Δ QTcF Time Course (unadjusted CIs).



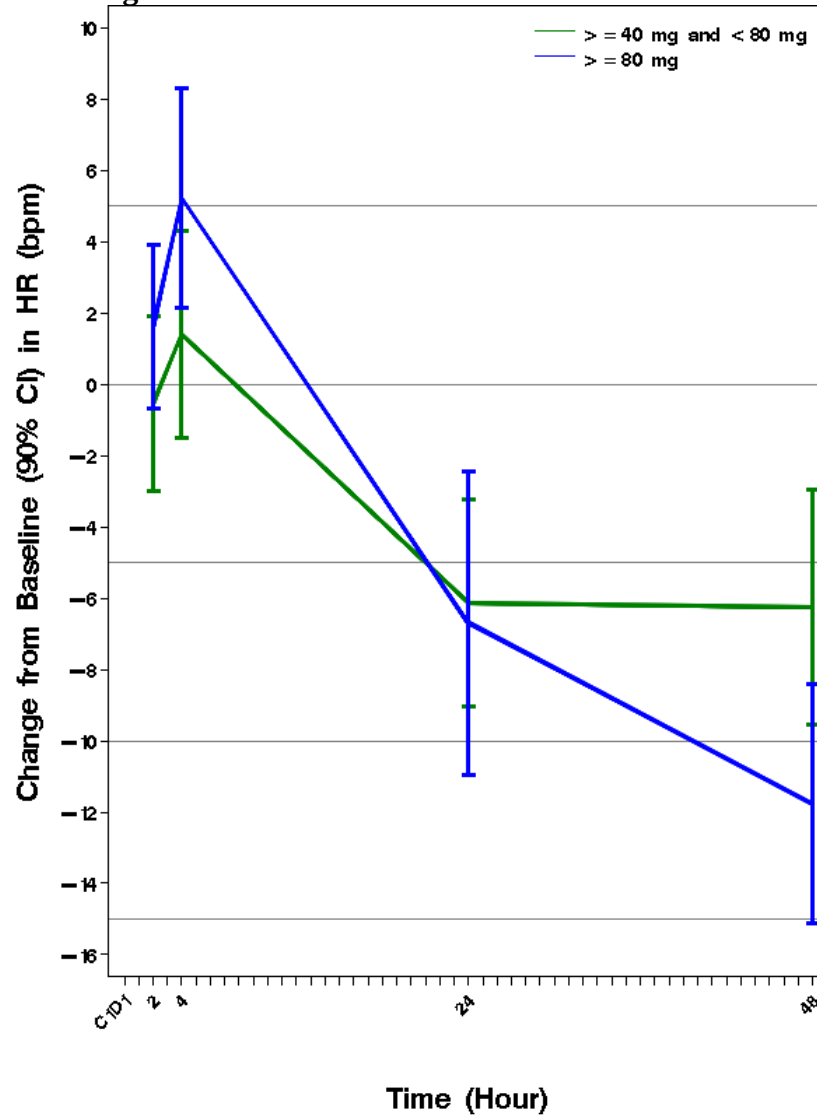
4.3.1.1 Assay sensitivity

Not Applicable

4.3.2 HR

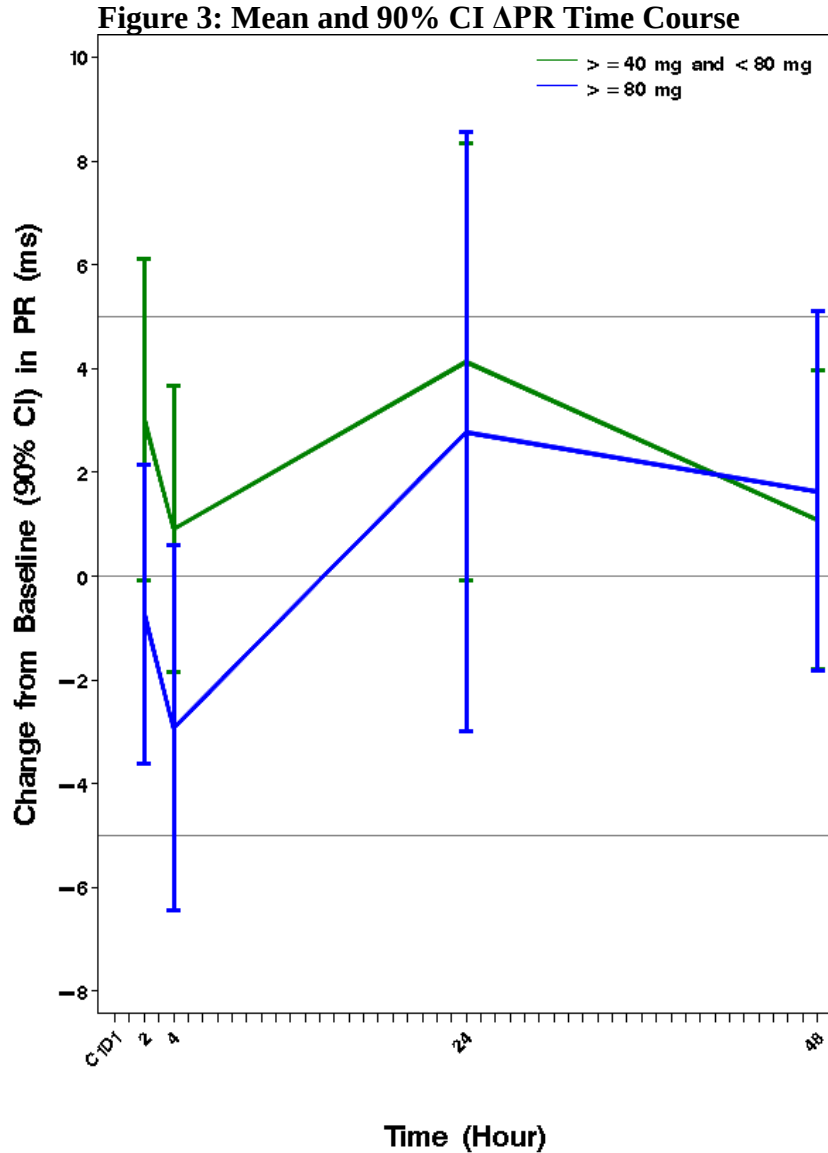
The same statistical analysis was performed based on HR (Figure 2). The largest upper limits of 90% CI for the mean change from baseline in HR (Δ HR) were 4.3 bpm and 8.3 bpm for ≥ 40 mg and < 80 mg and ≥ 80 mg dose groups, respectively. A large HR reducing effect was observed at 48 hours postdose for the selected data. Because of the short elimination half-life, selinexor exposure is minimal at 48 hours postdose. It is likely that the observed decrease in HR is not related to drug exposure, and it should not impact the interpretation of QTc interval around T_{max} (i.e. 2 hr postdose).

Figure 2: Mean and 90% CI Δ HR Time Course



4.3.3 PR

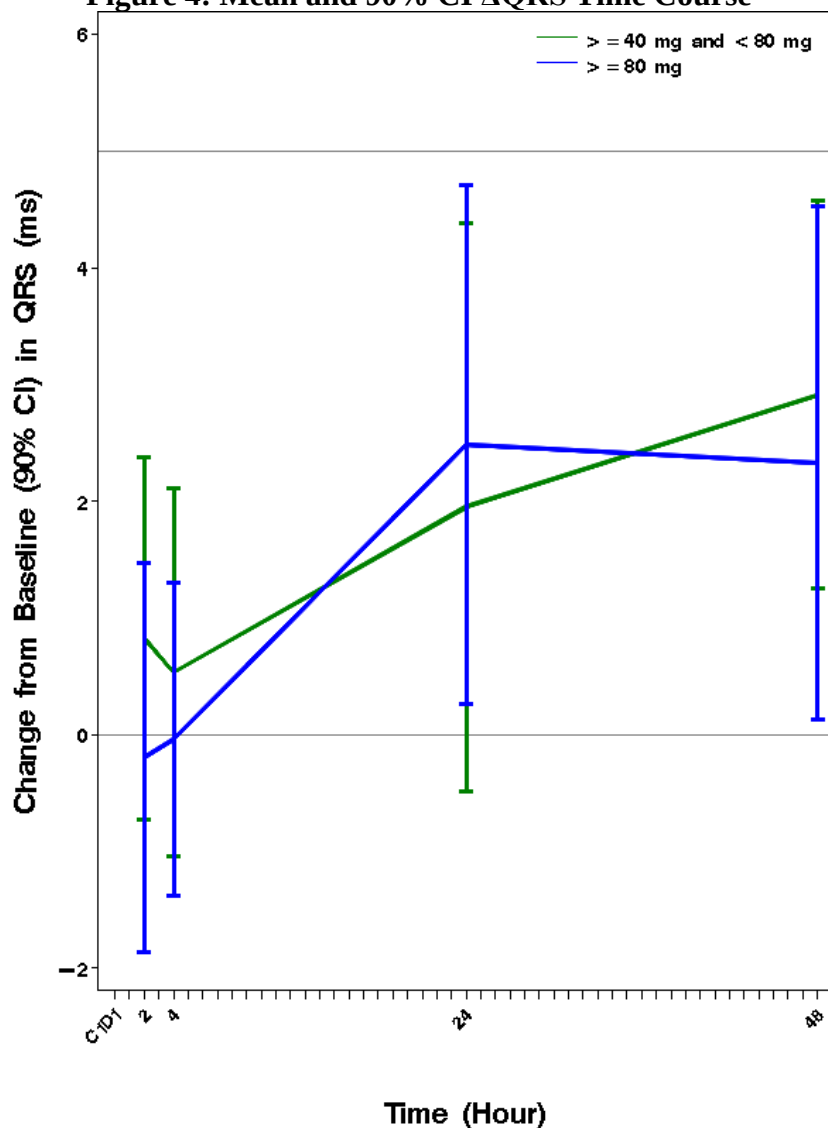
The same statistical analysis was performed based on PR interval (Figure 3). The largest upper limits of 90% CI for the mean change from baseline in PR (Δ PR) were 8.3 ms and 8.6 ms for ≥ 40 mg and < 80 mg and ≥ 80 mg dose groups, respectively.



4.3.4 QRS

The same statistical analysis was performed based on QRS interval (Figure 4). The largest upper limits of 90% CI for the mean change from baseline in QRS (Δ QRS) were 4.6 ms and 4.7 ms for ≥ 40 mg and < 80 mg and ≥ 80 mg dose groups, respectively. There were 11.6 % and 13.0% subjects who experienced QRS interval greater than 110 ms for the two dose groups, respectively.

Figure 4: Mean and 90% CI Δ QRS Time Course



4.4 CATEGORICAL ANALYSIS

4.4.1 QTc

All available data from safety population and from arms in which selinexor was administrated as monotherapy were included in categorical analysis. Table 5 lists the number of subjects as well as the number of observations whose QTcF values were between 450 ms and 480 ms, between 480 ms and 500 ms, or >500 ms.

Table 5: Categorical Analysis for QTcF

Study	Dose Group	Total N		450<QTcF<=480 ms		480<QTcF<=500 ms		QTcF>500 ms	
		Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
KCP-330-001	Baseline	140	140	14 (10.0%)	14 (10.0%)	3 (2.1%)	3 (2.1%)	1 (0.7%)	1 (0.7%)
	<40 mg	29	232	9 (31.0%)	29 (12.5%)	1 (3.4%)	1 (0.4%)	1 (3.4%)	1 (0.4%)
	>=40 mg and <80 mg	69	460	13 (18.8%)	41 (8.9%)	3 (4.3%)	8 (1.7%)	4 (5.8%)	10 (2.2%)
	>=80 mg	54	352	15 (27.8%)	45 (12.8%)	4 (7.4%)	4 (1.1%)	0 (0.0%)	0 (0.0%)
KCP-330-003	Baseline	21	21	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=40 mg and <80 mg	17	188	2 (11.8%)	4 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=80 mg	4	74	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 6 lists the categorical analysis results for Δ QTcF.

Table 6: Categorical Analysis of Δ QTcF

Study	Dose Group	Total N		30< Δ QTcF<=60 ms		Δ QTcF>60 ms	
		Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
KCP-330-001	<40 mg	29	232	6 (20.7%)	11 (4.7%)	1 (3.4%)	2 (0.9%)
	>=40 mg and <80 mg	64	435	12 (18.8%)	25 (5.7%)	4 (6.3%)	5 (1.1%)
	>=80 mg	52	342	9 (17.3%)	17 (5.0%)	2 (3.8%)	3 (0.9%)
KCP-330-003	>=40 mg and <80 mg	17	188	2 (11.8%)	3 (1.6%)	0 (0.0%)	0 (0.0%)
	>=80 mg	4	74	1 (25.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)

4.4.2 PR

The outlier analysis results for PR are presented in Table 7.

Table 7: Categorical Analysis for PR

Study	Dose Group	Total N		200<PR≤220 ms		PR>220 ms	
		Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
KCP-330-001	Baseline	140	140	3 (2.1%)	3 (2.1%)	2 (1.4%)	2 (1.4%)
	<40 mg	29	232	2 (6.9%)	2 (0.9%)	0 (0.0%)	0 (0.0%)
	≥40 mg and <80 mg	68	451	8 (11.8%)	14 (3.1%)	2 (2.9%)	6 (1.3%)
	≥80 mg	54	351	2 (3.7%)	5 (1.4%)	2 (3.7%)	4 (1.1%)
KCP-330-003	Baseline	21	21	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	≥40 mg and <80 mg	17	187	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	≥80 mg	4	74	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: The small differences in total N of Tables 3, 4 and 5 are caused by missing values for the specific ECG parameters.

4.4.3 QRS

The outlier analysis results for QRS are presented in Table 8.

Table 8: Categorical Analysis for QRS

Study	Dose Group	Total N		QRS≤110 ms		QRS>110 ms	
		Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
KCP-330-001	Baseline	141	141	126 (89.4%)	126 (89.4%)	15 (10.6%)	15 (10.6%)
	<40 mg	29	235	25 (86.2%)	209 (88.9%)	4 (13.8%)	26 (11.1%)
	≥40 mg and <80 mg	69	460	61 (88.4%)	412 (89.6%)	8 (11.6%)	48 (10.4%)
	≥80 mg	54	352	47 (87.0%)	319 (90.6%)	7 (13.0%)	33 (9.4%)
KCP-330-003	Baseline	21	21	21 (100%)	21 (100%)	0 (0.0%)	0 (0.0%)
	≥40 mg and <80 mg	17	188	17 (100%)	188 (100%)	0 (0.0%)	0 (0.0%)
	≥80 mg	4	74	4 (100%)	74 (100%)	0 (0.0%)	0 (0.0%)

4.4.4 HR

The outlier analysis results for HR are presented in Table 9.

Table 9: Categorical Analysis for HR

		Total N	HR≤100 bpm	HR>100 bpm	HR>45 bpm	HR≤45 bpm
Study	Dose Group	Subj. #	Subj. #	Subj. #	Subj. #	Subj. #
KCP-330-001	Baseline	140	120 (85.7%)	20 (14.3%)	140 (100%)	0 (0.0%)
	<40 mg	29	22 (75.9%)	7 (24.1%)	29 (100%)	0 (0.0%)
	≥40 mg and <80 mg	69	57 (82.6%)	12 (17.4%)	68 (98.6%)	1 (1.4%)
	≥80 mg	54	31 (57.4%)	23 (42.6%)	54 (100%)	0 (0.0%)
KCP-330-003	Baseline	21	19 (90.5%)	2 (9.5%)	21 (100%)	0 (0.0%)
	≥40 mg and <80 mg	17	11 (64.7%)	6 (35.3%)	17 (100%)	0 (0.0%)
	≥80 mg	4	4 (100%)	0 (0.0%)	4 (100%)	0 (0.0%)

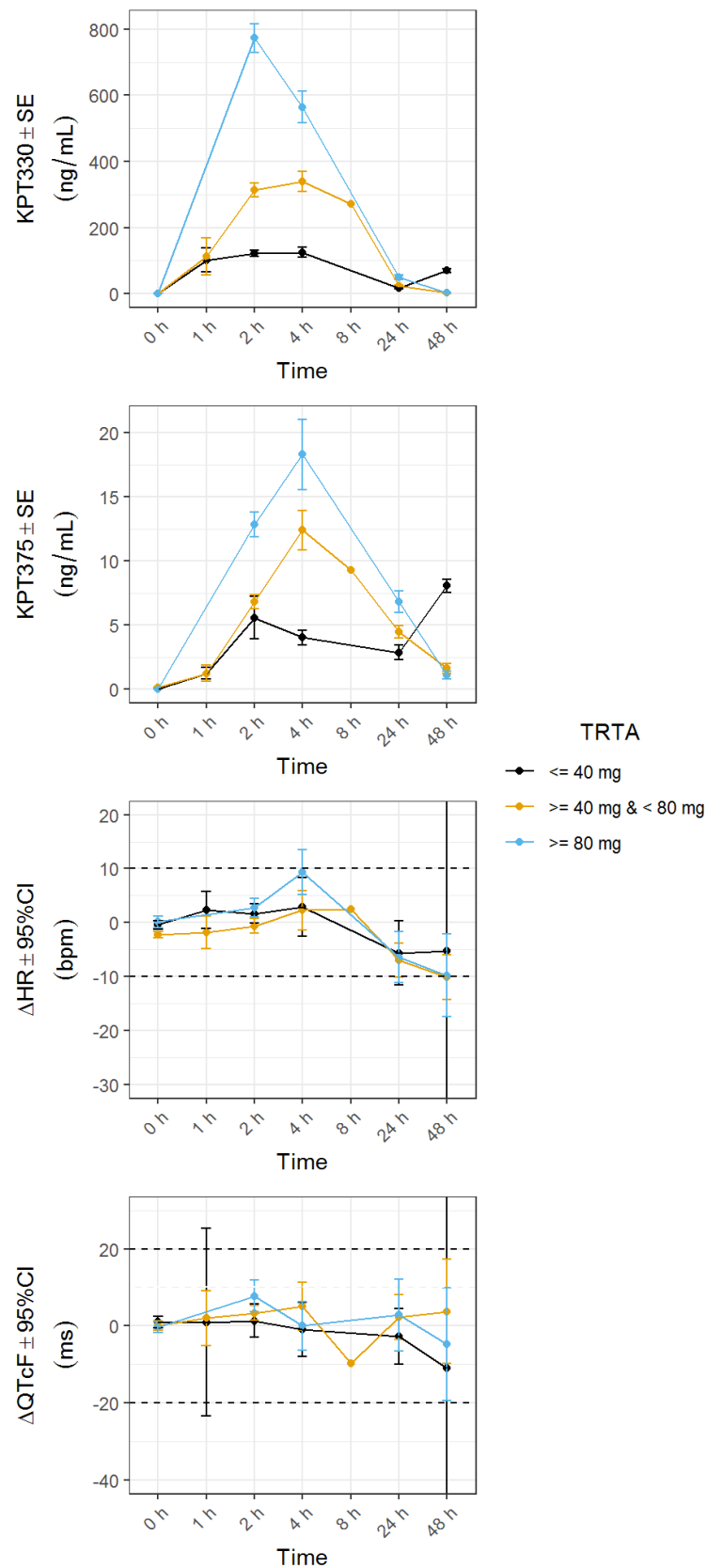
4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between selinexor concentration and ΔQTcF . Time-matched PK/ECG samples from a total of 83 patients in Study KCP-330-001 on selinexor monotherapy were included in the primary concentration-QTc analysis. 21 subjects received doses ≥ 80 mg.

Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and ΔQTcF and 3) presence of non-linear relationship. Figure 5 shows the time-course of drug concentration and changes in ΔHR and ΔQTcF . Because of minimal drug accumulation, observations were grouped by time-since-last-dose. Observations from different body-weight-based dosing regimen were grouped by actual dose for easy of evaluation of potential dose-dependent effect.

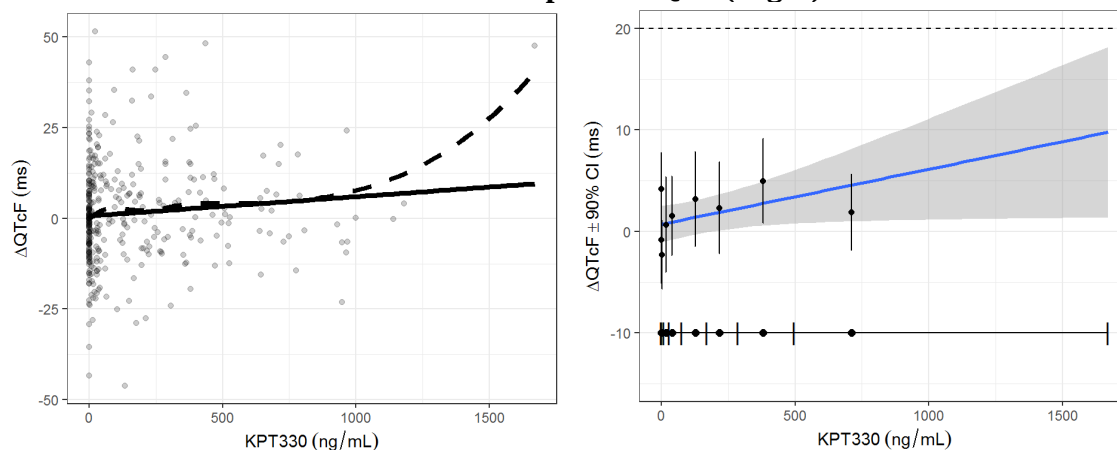
Despite of a large decrease at 48 hours postdose (when systemic exposure should be minimal given its short half-life), the figure suggests a small mean drug effect on HR at all other time points. There is an apparent dose-dependent increase in drug exposure and a trend of increasing ΔQTcF at T_{max} with higher selinexor dose. The figure does not show significant hysteresis, but the evaluation can be limited due to the small number of sampling time points.

Figure 5: Time course of drug concentration, heart rate and QTcF.



After confirming the absence of significant heart rate changes or delayed QTc changes, the scatter plot of ΔQTcF vs drug concentration was evaluated to determine if a linear model would be appropriate (Figure 6, Left). Despite of the single observation at the maximum concentration point, the figure supports the use of a linear model. The linear model was applied to the data and the goodness-of-fit plot is shown in Figure 6 (Right). The linear model ($\Delta\text{QTcF} \sim 1 + \text{CONC} + \text{Baseline_adjustment}$, with USUBJID as a random effect on intercept and slope) suggests a positive relationship between ΔQTcF vs drug concentration, however, the upper bound of 90% confidence interval for ΔQTcF is less than 20 ms (4.4 ms, 90% CI [1.0 ms, 7.8 ms]) at the predicted C_{max} (i.e. 80 mg, $C_{\text{max}} = 680 \text{ ng/mL}$ [Summary of Clinpharm, Module 2.7, Submission 0003]).

Figure 6: Assessment of linearity of concentration-QTc relationship (Left) and Goodness-of-fit plot for QTc (Right)



In the PK/ECG dataset that were used to support the primary exposure-response analysis, approximately 30% of ECG/PK data were collected more than 30 min apart. In a sensitivity analysis excluding these observations, the predicted slope and ΔQTcF at the therapeutic dose are very close to those derived from the primary exposure-response analysis. The inclusion of data from study KCP-330-003 resulted in similar prediction. Overall, exposure-response analysis suggests a lack of large mean effect on ΔQTcF at the therapeutic dose level.

4.5.1 Assay sensitivity

Not applicable.

4.6 SAFETY ASSESSMENTS

See section 3.2.3.

4.7 OTHER ECG INTERVALS

No clinically significant changes in PR or QRS were observed.

5 APPENDIX

5.1 IRT'S HIGHLIGHT OF CLINICAL PHARMACOLOGY AND CARDIAC SAFETY

Therapeutic dose	80 mg taken weekly together with dexamethasone 20 mg, on Days 1 and 3.	
MTD	120 mg taken weekly on Days 1 and 3.	
Principal adverse events	The most common non-hematological TE AEs are nausea (72.9%), fatigue (66.8%), decreased appetite (53.7%), decreased weight (46.3%), diarrhea (44.4%), vomiting (41.1%), hyponatremia (38.3%), dyspnea (24.8%), constipation (24.3%). The most commonly reported hematological treatment-emergent AEs are thrombocytopenia (73.8%), anemia (59.3%), neutropenia (34.6%), leukopenia (28.0%) and lymphopenia (15.0%).	
Maximum dose tested and Exposures Achieved	Single Dose	80 mg/m ² . Mean (%CV) Cmax: 1175 ng/mL (54%) and Mean (%CV) AUC: 5788 ng*h/mL (34%)
	Multiple Dose	80 mg/m ² taken weekly on Days 1 and 3. Exposure reported for 45 mg/m ² dose, Cmax: 542 ng/mL (23%)
Range of linear PK	3 mg/m ² to 80 mg/m ²	
Accumulation at steady state	No evidence of substantial plasma selinexor accumulation following 2 or 3 weeks of twice or 3 times weekly oral administration of selinexor. Pre-dose plasma selinexor concentrations on Day 15, 17, 19, or 22 (48 hours following the previous dose) for the majority of patients. Average concentrations from time 0-8 hours were consistent with those on Day 1.	
Metabolites	Selinexor is the major circulating moiety in human plasma. The limited metabolism of selinexor is catalyzed by multiple enzymes, including CYP3A4, UGTs, and GSTs. The metabolites include KPT-375 (minimal biological activity, <5% of peak of parent levels), and at lower levels, inactive N-dealkylation, glucuronidation and glutathione conjugations.	
Absorption	Bioavailability	The oral bioavailability of the compound was high (F ~61-67%) in both rat and monkey.
	Tmax	Median (range) for parent: 2 [0.5, 4.0] hours on day 1 at the highest dose of 80 mg/m ² and is consistent with estimates across dose levels. Median (range) for metabolites has not been determined in humans.
Distribution	Vd/F or Vd	1.14 and 1.44 and 1.5 L/kg, in rat monkey and humans.
	% bound	The mean values for the unbound fraction in rat, monkey, and human plasma were 4%, 4%, and 5%, respectively.
Elimination	Route	Selinexor has not been studied in definitive radiolabel mass balance study; however, based on cold metabolism assessment and rat [14C]-selinexor study, it is presumed that selinexor is excreted by hepatobiliary route into feces with minimal excretion into urine.
	Terminal t _{1/2}	Parent drug: 5.5 hr. Metabolites: not determined.
	CL/F or CL	0.19 to 0.24 L/h/kg in humans.
Intrinsic Factors	Age, Sex, Race	Age (18 to 65 years old), Gender (male n= 422, female n= 298), and Race/ethnicity had no clinically significant effect on the pharmacokinetics of selinexor, based on population PK covariate analysis (n=720).
	Hepatic & Renal Impairment	No dose adjustment is needed in patients with mild to severe hepatic impairment according to NCI-Organ Dysfunction Working Group criteria based on population PK covariate

		analysis. The CL/F was 16.75 vs 16.77 L/hr in normal (n=611) compared to the severe group (n=3). No dose adjustment is necessary for patients with mild (CLcr: 60-89 mL/min, n=277) to severe (CLcr: 15-29 mL/min, n=15) renal impairment. The CL/F in was 17.56 vs 16.37 L/hr in normal (n=261) compared to the severe group (n=15).
Extrinsic Factors	Drug interactions	No human formal DDI studies have been performed to date. Selinexor has a low potential for drug-drug interactions in humans because it is a substrate of multiple metabolic enzymes, and the compound underwent direct excretion in rats. Selinexor is not a substrate for major metabolic transporters. In population PK analyses, the impact of concomitant drugs on selinexor exposure was evaluated. There were 143 patients who had concomitant medications which are CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, fluconazole, etc). The exposures to selinexor were not altered in the presence of any of the major human CYP modifiers, including CYP3A4 inhibitors or inducers. Patients also received comedications which are inhibitors of CYP2C9/19 (e.g., fluconazole), CYP2D6 (e.g., bupropion, paroxetine, terbinafine), and CYP1A2 (e.g., ciprofloxacin). No overt differences in PK leading to adverse events (AEs) were observed for selinexor and no major changes in the AE profile of these (or other concomitant) drugs were reported.
	Food Effects	Selinexor can be administered with or without food.
The supra-therapeutic dose has not been identified. <i>Reviewer's comment: In popPK analysis, the sample size is very small in patients with moderate or severe HI. The popPK analysis does not support the conclusion of low DDI potential. A PMR/PMC study is under consideration to evaluate high exposure scenario.</i>		
Preclinical Cardiac Safety	Selinexor inhibited hERG with an IC50 value of 20.6 µM. The IC50 value, based on human plasma protein binding of 95.1% and mean Cmax of 1.53 µM, is estimated to be ~250X higher than the free unbound Cmax of 0.07 µM following an 80 mg dose. In the in vivo cardiovascular assessment in 4-week and 13-week toxicity studies, selinexor showed no AEs in the cardiovascular system in monkeys.	
Clinical Cardiac Safety	The potential for selinexor to prolong the QTc interval was assessed using data collected from Studies KCP-330-001 and KCP-330-003 (n=85). The time-matched plasma concentrations from these studies enabled the assessment of QT changes over time and concentration-QTc (C-QTc) interval relationship (KS-50042). No clear relationship by dose levels was observed between ΔQTcF and selinexor concentrations. Linear mixed-effect modeling demonstrated a small positive slope such that a selinexor concentration of 1200 ng/mL (~2-fold higher than anticipated therapeutic concentrations) correlates with a potential mean ΔQTcF increase of 7.2 msec, with a 90% CI of <20 msec increase above baseline. Therefore, selinexor is not expected to cause clinically relevant QTc prolongation at the therapeutic dose concentrations of selinexor and predict that the QTcF will remain within 20 msec of baseline. Additionally, none of the patients had a ΔQTcF of >60 msec in the PK population.	

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/s/

NAN ZHENG
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CHRISTINE E GARNETT
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Division of Hematology Products (DHP) Labeling Review

NDA/BLA Number	NDA 212306
Supporting Document Number	3
Proprietary Name (proposed) (nonproprietary name)	XPOVIO (selinexor)
Receipt Date	08/06/18
PDUFA Goal Date (Internal Goal Date)	04/06/19
Review Classification	Priority
Proposed Indication (or current indication if unchanged)	For the treatment of patients with relapsed refractory multiple myeloma (RRMM) who have received at least 3 prior therapies and whose disease is refractory to at least 1 proteasome inhibitor (PI), at least 1 immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody (mAb)
Dosing Regimen	80 mg Days 1 and 3 per week (in combination with 20 mg dexamethasone)
From	Virginia Kwitkowski, MS, ACNP-BC Associate Director for Labeling, DHP

Background of Application:

Karyopharm Therapeutics have submitted a New Drug Application per 21 CFR 314.510 Subpart H, requesting accelerated approval for selinexor for the treatment of patients with relapsed refractory multiple myeloma who have received at least 3 prior therapies and are refractory to at least 1 proteasome inhibitor, 1 IMiD, and 1 anti-CD38 monoclonal antibody. Selinexor is an oral, first-in-class selective inhibitor of nuclear export (SINE) that blocks exportin 1 (XPO1). The application is primarily based on a single-arm Phase 2b trial [KCP-330-012/STORM] providing response rate data in patients with triple class refractory MM who received selinexor 80 mg plus dexamethasone 20 mg twice weekly on Days 1 and 3 every week in 4 week cycles. This trial is ongoing but enrollment is complete with 123 patients enrolled to Part B and 79 enrolled to Part A. The Applicant claims that pharmacokinetic parameters of selinexor were not substantially altered in patients with various degrees of hepatic or renal impairment. Body mass index was also a significant covariant for clearance with lean patients having a lower clearance and obese patients having a higher clearance. The difference in clearance due

to BMI was not considered clinically relevant as it represented <40% difference. There was more nausea and vomiting in female patients with a 19% reduced clearance in female patients. The incidence of grade 3 and greater AEs were correlated with exposure for the events of thrombocytopenia, hyponatremia, and fatigue. There does not appear to be a clinically relevant effect of selinexor on the QTc interval.

For patients with penta-exposed, triple class refractor MM from Study KCP-330-012 (Parts 1 or 2) the ORR per IRC was 25.4% (including 2 patients with sCR/CR).

The proposed confirmatory trial is ongoing (KCP-330-023/BOSTON) and is a randomized trial comparing Velcade 1.3 mg/m² twice weekly plus Dexamethasone 20 mg 4x weekly ± selinexor 100 mg weekly. The primary endpoint for the BOSTON trial is PFS. At the time of submission, 37 of the planned 364 patients have enrolled. Crossover of patients randomized to the control arm are permitted to crossover at the time of progressive disease.

Documents Reviewed:

Module 1: Cover Letter, Draft Labeling

Module 2: Clinical Summary, Clinical Overview

Module 5: Clinical Study Report (KCP-330-012) Phase 2b study in RRMM

In this review, I propose labeling recommendations and edits in the XPOVIO labeling to ensure that the prescribing information is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of XPOVIO.

The following pages contain the working version of the XPOVIO labeling with my recommended edits and comments (identified as 'KV1' through 'KV43') and includes comments and edits from other review team members. Given that the scientific review of the labeling is ongoing, my labeling recommendations in this review should be considered preliminary and may not represent DHP's final recommendations for the XPOVIO labeling.

26 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

VIRGINIA E KWITKOWSKI
12/03/2018

CLINICAL INSPECTION SUMMARY

Date	October 30, 2018
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Andrea Baines, M.D., Medical Officer Vishal Bhatnagar, M.D., Clinical Team Leader Ann Farrell, M.D., Director Thomas Iype, Pharm.D., Regulatory Project Manager Division of Hematology Products
NDA	212306
Applicant	Karyopharm Therapeutics, Inc.
Drug	Selinexor
NME	Yes
Therapeutic Classification/Status	Selective inhibitor of nuclear export (SINE) compound
Proposed Indication	Treatment of patients with relapsed or refractory multiple myeloma
Consultation Request Date	August 6, 2018 (Priority Review)
Summary Goal Date	December 1, 2018
Action Goal Date	April 6, 2019
PDUFA Date	April 6, 2019

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical sites (Drs. David Dingli, Dan Vogl, and Sundar Jagannath) were selected for inspection in support of NDA 212306. The study data from these clinical sites, as reported by the sponsor to the NDA, are considered to be reliable in support of the requested indication.

The preliminary regulatory classification of Dr. Dingli is No Action Indicated. The regulatory classification of Dr. Vogl is No Action Indicated. The regulatory classification of Dr. Jagannath is Voluntary Action Indicated.

2. BACKGROUND

Tumor suppressing proteins (TSPs) have been identified in cancer pathogenesis, including but not limited to tumor protein 53 (TP53), FOXO3a (a Forkhead box O-class [FOXO] transcription factor), breast cancer susceptibility gene 1 (BRCA1), protein phosphatase 2A (PP2A), and retinoblastoma protein (Rb). Selinexor is an oral, first in class, slowly reversible, potent selective inhibitor of nuclear export (SINE) compound that specifically blocks the XPO1 (Exportin-1) protein. Selinexor restores many of the tumor suppressing proteins to the nucleus where they can carry out their normal functions. The combination of selinexor and dexamethasone is reported to be synergistic in vitro and in vivo in multiple myeloma cell cytotoxicity assays through increased nuclear localization of glucocorticoid receptor (GR) and amplified GR transcriptional activity.

The sponsor proposes that selinexor in combination with dexamethasone be used for the treatment of patients with relapsed or refractory multiple myeloma (RRMM) who have received at least three prior therapies and whose disease is refractory to at least one proteasome inhibitor (PI), at least one immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody (mAb).

The review division (DHP) requested three clinical study site inspections for Study KPC-330-012.

Study KPC-330-012/STORM

Study KPC-330-012/STORM is a Phase 2b, multicenter, single-arm, 2-part, open-label study designed to evaluate the efficacy and safety of selinexor with dexamethasone, in patients with quad-exposed-double-class-refractory, or penta-exposed-triple-class-refractory multiple myeloma. The primary study objective is to evaluate the efficacy of selinexor 80 mg orally (PO) plus low-dose dexamethasone 20 mg PO on Days 1 and 3 twice-weekly in patients with penta-exposed, triple-class-refractory, multiple myeloma enrolled in Part 2 of the study.

The primary efficacy endpoint is the overall response (ORR [Responses based on IRC Assessment per International Myeloma Working Group (IMWG) Criteria]). The response is defined as the proportion of patients who achieved the composite treatment responses (Stringent Complete Remission [sCR], Complete Remission [CR], Very Good Partial Response [VGPR], or Partial Response [PR]), using the modified intent-to-treat (mITT) population, defined as Part 2 patients with penta-exposed-triple-class-refractory multiple myeloma who received at least one dose of study treatment.

Subjects were enrolled at 60 sites across six countries. A total of 203 patients were enrolled. The first patient enrolled on May 26, 2015; the last patient enrolled on March 23, 2018. The study is ongoing.

3. RESULTS (by site):

Name of Clinical Investigator/Address	Protocol #/ Site #/ # Subjects enrolled	Inspection Dates	Classification
Dr. David Dingli 200 First St SW Rochester, MN 55905	Study KPC-330-012 Site #16 22 subjects	October 9 - 12, 2018	Preliminary NAI*
Dr. Sundar Jagannath 1470 Madison Ave New York, NY 10029	Study KPC-330-012 Site #21 34 subjects	September 19 - 21, 2018	VAI
Dr. Dan Vogl P.C.A.M., 2nd Floor West Pavilion 3400 Civic Center Blvd. Philadelphia, PA 19104	Study KPC-330-012 Site #26 16 subjects	October 3 - 12, 2018	NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data are unreliable.

* Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Investigator**1. David Dingli, M.D.**

A total of 25 subjects were screened and 22 subjects were enrolled. All subjects received and completed study treatment. The study is ongoing.

For this inspection, a complete review of all regulatory documentation at the study site was performed, as well as the source records for 13 subjects enrolled at the site prior to the database lock. A 100% review of informed consent forms was completed. The source records reviewed included medical records, regulatory binder documents, source data worksheets, informed consent forms, monitoring follow-up reports, and pharmacy records.

Source documents for the 13 enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings for primary efficacy endpoints, adverse events and serious adverse event reporting. A complete compliance review was conducted for 10 study subject records. Source documents for the raw data used to assess the primary safety study endpoint were verifiable at the study site. There was no under-reporting of adverse events noted during this site audit. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

2. Sundar Jagannath, M.D.

A total of 37 subjects were screened and 34 subjects were enrolled. Thirty-three subjects completed the treatment phase of this study. The study is ongoing.

The inspection evaluated the following documents: source records, screening and enrollment logs, physician clinical notes, eligibility criteria, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for 18 enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings for primary study endpoint assessment, adverse event and serious adverse event reporting. A 100% review of the informed consent documentation was conducted for the 34 enrolled study patients. Records review of 18 subjects indicated that the eligibility criteria for enrollment were met. Source documents for the raw data used to assess the primary safety study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. However, a Form FDA 483 was issued at the completion of the inspection for failure to maintain accurate case histories (This List of Inspectional Observations was shared with DHP). Specifically, 10 study subjects' concomitant medications in source records were not recorded accurately, adequately and completely in the subjects' electronic CRFs. While these protocol violations for this single-arm, open-label study were regulatory deficiencies, the incomplete listing of concomitant medications was not considered significant.

Subject #	Concomitant medications
(b) (6)	ciprofloxacin, sodium bicarbonate
	guaifenesin, capsaicin, calcium with vitamin D ₂ , magnesium oxide
	tretinoin, fluticasone, diazepam, levothyroxine
	darbepoetin alfa
	ondansetron, human immune globulin injection, multivitamins, prochlorperazine
	biotin
	cetirizine, oxycodone with acetaminophen
	aspirin, Lactobacillus probiotics, multivitamins, calcium with vitamin D ₃
	levocarnitine
	umeclidinium, levalbuterol, zoledronic acid

The principal site investigator responded adequately to the observations in a letter received on October 4, 2018. As part of the preventive and corrective action plan, a concomitant medication log was introduced in the source medical record progress note. In addition, the clinical study site data team will meet with the clinicians on a weekly basis, to clarify and to confirm any medications/supplements that remain to be resolved by the research site team.

3. Dan Vogl, M.D.

A total of 22 subjects were screened and 16 subjects were enrolled. Eleven subjects completed the treatment phase of this study (five patients discontinued due to adverse events). The study is ongoing.

The inspection evaluated the following documents: source records, screening and enrollment logs, physician clinical notes, eligibility criteria, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for 16 enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings for patient informed consent documentation, primary study endpoint assessment, adverse event and serious adverse event reporting. A comprehensive audit of the inclusion and exclusion criteria for patient enrollment was evaluated at this site inspection. Source documents for the raw data used to assess the primary safety study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. No Form FDA 483 was issued.

{See appended electronic signature page}

Anthony Oencia, M.D.

Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.

Branch Chief, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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