CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211155Orig1s000
211155Orig2s000

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:	September 10, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 211155
Product Name and Strength:	Copiktra (duvelisib) Capsules
Applicant/Sponsor Name:	Verastem
FDA Received Date:	August 22, 2018 and September 5, 2018
OSE RCM #:	2018-297-2
DMEPA Safety Evaluator:	Leeza Rahimi, Pharm.D.
DMEPA Team Leader:	Hina Mehta, Pharm.D.

1 PURPOSE OF MEMORANDUM

Division of Hematology Products (DHP) requested that we review the revised carton and container for Copiktra (duvelisib) (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] (b) (4) (b) (4)

2 CONCLUSION

The revised carton and container labels for Copiktra are acceptable from a medication error perspective. We have no further recommendations at this time.

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[a] Rahimi, L. Label and Labeling Review for Copiktra (NDA 211155). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUL 20. RCM No.: 2018-297-1.

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/s/

LEEZA RAHIMI
09/10/2018

HINA S MEHTA
09/11/2018

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:	August 27, 2018
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nisha Patel, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	COPIKTRA (duvelisib)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 211155
Applicant:	Verastem Inc.

1 INTRODUCTION

On February 5, 2018, Verastim Inc. submitted for the Agency's review an original New Drug Application (NDA) 211155 for COPIKTRA (duvelisib) capsules. The proposed indications for COPIKTRA (duvelisib) capsules are for the treatment of patients with:

- Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL), (b) (4)
- Follicular B-cell Non-Hodgkin Lymhoma (FL) who have received at least two prior therapies.

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 March 21, 2018 and February 28, 2018 respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for COPIKTRA (duvelisib) capsules.

2 MATERIAL REVIEWED

- Draft COPIKTRA (duvelisib) capsules MG received on March 2, 2018, further revised and received by DMPP on August 16, 2018.
- Draft COPIKTRA (duvelisib) capsules Prescribing Information (PI) received on February 5, 2018 and revised on March 2, 2018, revised by the Review Division throughout the review cycle, and received by DMPP on August 15, 2018.
- Approved ZYDELIG (idelasilib) comparator labeling dated February 2, 2018.

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 MG.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
08/27/2018

NISHA PATEL
08/27/2018

LASHAWN M GRIFFITHS
08/27/2018

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

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

Memorandum

Date: August 21, 2018

To: Rachel McMullen, Regulatory Project Manager
Division of Hematology Products (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Mathilda Fienkeng, Team Leader, OPDP

Subject: OPDP Labeling Comments for COPIKTRA (duvelisib capsules), for oral use

NDA: 211155

In response to DHP's consult request dated February 28, 2018, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for the original NDA submission for COPIKTRA (duvelisib capsules), for oral use (Copiktra).

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI and Medication Guide emailed to OPDP on August 14, and August 16, 2018, respectively, 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.

Thank you for your consult. If you have any questions, please contact Nisha Patel at (301) 796-3715 or nisha.patel@fda.hhs.gov.

Product Labeling

Section	Statement from draft	Comment
Highlights, Boxed Warning Boxed Warning	(b) (4) pneumonitis occurred in 5% of COPIKTRA-treated patients. Monitor for pulmonary symptoms and interstitial infiltrates (emphasis added).	We note that the Warnings and Precautions section of the full PI states, "**Serious, including fatal** (1/442; <1%), pneumonitis without an apparent infectious cause occurred in 5% of patients receiving COPIKTRA 25 mg BID (N = 442)" (emphasis added). OPDP recommends revising the Boxed Warning sections to include "fatal and/or serious" pneumonitis for consistency with the Warnings and Precautions section.
5 Warnings and Precautions, 5.1 Infections	If COPIKTRA is resumed, (b) (4) (b) (4) and monitor patients for CMV reactivation by PCR or antigen test at least monthly (emphasis added).	We note that Table 1 from the full PI states, "Resume at the **same or reduced dose**. If COPIKTRA is resumed, monitor patients for CMV reactivation (by PCR or antigen test) at least monthly" (emphasis added) for "Clinical CMV infection or viremia (positive PCR or antigen test)." Should "same" be added to Section 5.1 for consistency with Table 1?
5 Warnings and Precautions, 5.3 Cutaneous Reactions	Withhold COPIKTRA for severe (Grade 3) cutaneous reaction until resolution. Initiate supportive care with **steroids (topical or systemic)** or anti-histamines (for pruritus) (emphasis added).	We note that Table 1 from the full PI states, "Initiate supportive care with **emollients**, anti-histamines (for pruritus), or **topical steroids**" (emphasis added) for "Cutaneous Reactions Grade 3." Should Section 5.3 be revised for consistency with Table 1?
6 Adverse Reactions, 6.1 Clinical Trial Experience, Summary of Clinical Trial Experience in B-cell Malignancies	Table 4 Most Common New or Worsening Laboratory Abnormalities (≥ 20% Any Grade) in Patients with B-cell Malignancies Receiving COPIKTRA	Should N=442 be included for Table 4?
6 Adverse Reactions, 6.1 Clinical Trial Experience, Summary of Clinical Trial Experience in FL	The most common adverse reactions (≥ 20% of patients) were diarrhea or colitis, nausea, fatigue, musculoskeletal pain, rash, neutropenia, cough, anemia, pyrexia, headache, mucositis, abdominal pain, vomiting, transaminase elevation, and thrombocytopenia.	Please consider including the incidence rates for these common adverse reactions since a corresponding table is not being included in the full PI for the relapsed or refractory FL population. This information would provide important contextual risk information for

Section	Statement from draft	Comment
		promotional materials.
17 Patient Counseling Information	(b) (4)	We note that the Boxed Warning and/or Warnings and Precautions section of the full PI states that each of these adverse reactions were "serious, including fatal." OPDP recommends including this risk information.
17 Patient Counseling Information		Please consider including patient counseling information regarding the Warning and Precaution, Hepatoxicity.
17 Patient Counseling Information	Advise females of reproductive potential to use effective contraception during treatment and (b) (4) after receiving the last dose of COPIKTRA.	We note that the Warnings and Precautions section of the full PI states, "Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment and for **at least** 1 month after the last dose" (emphasis added). We recommend revising this statement for consistency with the Warnings and Precautions section.

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/s/

NISHA PATEL
08/21/2018

Office of Prescription Drug Promotion

Internal Consults

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

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.

To: Kate Heinrich Oswell, Health Communications Analyst,
Division of Risk Management (DRISK),
Office of Surveillance and Epidemiology (OSE)

From: Nisha Patel, Regulatory Review Officer, OPDP

CC: Mathilda Fienkeng, Team Leader, OPDP
Neil Vora, Safety Regulatory Project Manager, OSE
Elizabeth Everhart, Team Leader, DRISK
Joyce Weaver, Risk Management Analyst, DRISK
Doris Auth, Associate Director, DRISK
Carole Broadnax, OPDP
Michael Wade, OPDP
CDER-OPDP-RPM

Date: August 1, 2018

Re: NDA 211155
COPIKTRA (duvelisib capsules), for oral use
Comments on draft Risk Evaluation and Mitigation Strategies (REMS)
Materials (Submission date: June 29, 2018)

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for COPIKTRA:

- Healthcare Provider (HCP) REMS Materials:
  - Dear Healthcare Provider letter
  - Professional Society REMS letter
  - REMS Fact Sheet

- Direct-to-Consumer (Patient) REMS Materials:
  - Patient Safety Wallet Card

- COPIKTRA REMS Program website

The version of the draft REMS materials used in this review were sent from DRISK (Kate Heinrich Oswell) via email on July 17, 2018. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for COPIKTRA.

General Comments

Please remind Verastem, Inc. that REMS materials are not appropriate for use in a promotional manner.

OPDP notes the link www.COPIKTRAREMS.com, and toll free numbers (b) (4) (b) (4) and 1-877-779-8786. OPDP recommends that these items represent a direct link to only REMS related information and not be promotional in tone. Furthermore, we remind Verastem, Inc. that the REMS specific website should not be the sole source of approved REMS materials.

OPDP notes that the Copiktra Prescribing Information (PI) and Medication Guide are still being reviewed and modified. Therefore, we recommend that the REMS materials be revised, as appropriate, to reflect all changes in the final approved Copiktra PI and Medication Guide. Please note that as the Boxed Warning, Indications and Usage, and Warnings and Precautions sections of the Copiktra PI are still under review, OPDP has not provided specific comments below on related sections in the REMS materials.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see Specific Comments below):

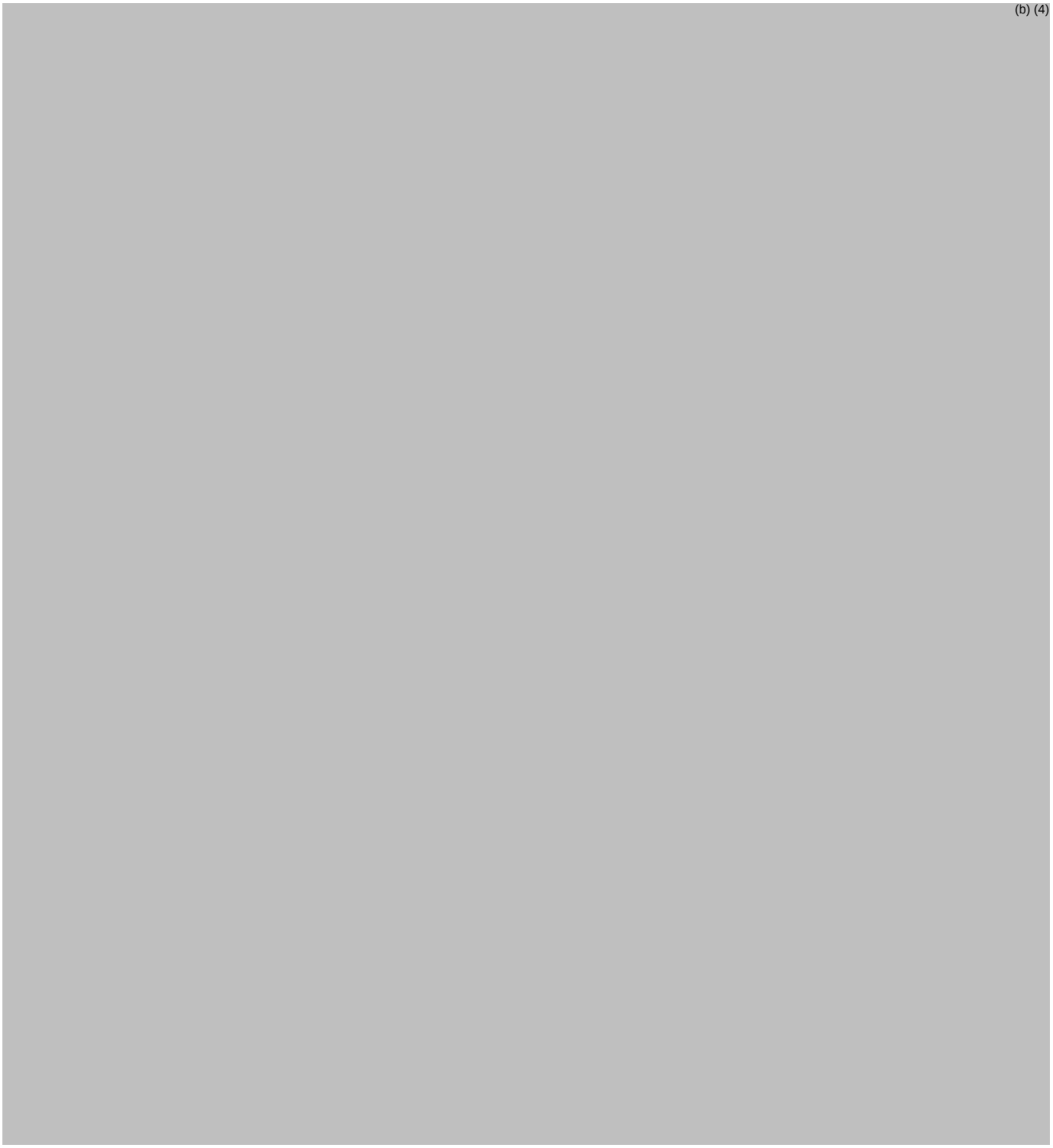
- Dear Healthcare Provider letter
- Professional Society REMS letter
- REMS Fact Sheet

- Patient Safety Wallet Card
- COPIKTRA REMS Program Website

Specific Comments

OPDP considers the following statements promotional in tone and recommends revising or deleting them from the REMS piece:

(b) (4)



We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

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/s/

NISHA PATEL
08/01/2018

Division of Hematology Products (DHP) Labeling Review

NDA Number	**NDA 211155**
Proprietary Name **(nonproprietary name)**	**Copiktra (duvelisib)**
Receipt Date	**02/05/2018**
PDUFA Goal Date **(Internal Goal Date)**	**10/05/18**
Review Classification	**Priority**
Proposed Indication (or current indication if unchanged)	**CLL/SLL,** (b) (4) (b) (4) **Follicular B-cell non-Hodgkin lymphoma who have received at least two prior therapies**
Dosing Regimen	**25 mg orally, twice daily**
From	**Virginia Kwitkowski, MS, ACNP-BC** **Associate Director for Labeling, DHP**

Background of Application: (example text below)

The NDA for duvelisib (COPIKTRA), a kinase inhibitor, was submitted on February 05, 2018. The Applicant is seeking approval in patients with CLL/SLL and Follicular Lymphoma as specified above. In support of the CLL/SLL indication, the Applicant conducted a single randomized, open-label, actively controlled trial (NCT02004522) in 319 adult patients with CLL after at least one prior line of therapy. The control arm was Arzerra (ofatumumab). In support of the Relapsed Follicular Lymphoma indication, the applicant submitted a single, single-arm trial in 83 patients with Follicular Lymphoma who were refractory to rituximab and to either chemotherapy or radioimmunotherapy.

In this review, I propose labeling recommendations and edits in the COPIKTRA 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 COPIKTRA.

The following pages contain the working version of the COPIKTRA labeling with my recommended edits and comments (identified as 'KV2' through 'KV69') and include comments and edits from other disciplines. 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 COPIKTRA labeling.

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/s/

VIRGINIA E KWITKOWSKI
07/30/2018

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 26, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 211155
Product Name and Strength:	Copiktra (duvelisib) Capsules
Applicant/Sponsor Name:	Verastem
FDA Received Date:	July 20, 2018
OSE RCM #:	2018-297-1
DMEPA Safety Evaluator:	Leeza Rahimi, Pharm.D.
DMEPA Team Leader:	Hina Mehta, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Division of Hematology Products requested that we review the revised carton and container labeling for Copiktra (duvelisib) Capsules (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] (b) (4) (b) (4)

2 CONCLUSION

The revised container bottle labels for Copiktra are acceptable from a medication error perspective. However, the revised blister packer, inner sleeve and outer sleeve requires additional revisions to prevent confusion and minimize the risk of dosing errors. (b) (4) (b) (4) (b) (4). We recommend the product strength on the principal display panel and other panels of the blister carton labeling describe the milligram amount of drug (i.e. 15 mg per capsule).

[a] Rahimi, L. Label and Labeling Review for Copiktra (NDA 211155). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 12. RCM No.: 2018-297.

3 RECOMMENDATIONS FOR VERASTEM

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

A. Blister packer, Inner Sleeve, and Outer Sleeve

1. The product strength should be expressed per single unit (i.e. 15 mg per capsule) when the package does not immediately make it clear that the designated strength is per unit per Draft Guidance: Container and Carton, April 2013 (lines 586-591). Please revise blister packer and inner and outer sleeve accordingly.

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/s/

LEEZA RAHIMI
07/27/2018

HINA S MEHTA
07/27/2018

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:	June 12, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 211155
Product Name and Strength:	Copiktra (duvelisib) capsules
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription
Applicant/Sponsor Name:	Versatem
FDA Received Date:	February 05, 2018, March 22, 2018
OSE RCM #:	2018-297
DMEPA Safety Evaluator:	Leeza Rahimi, Pharm.D.
DMEPA Team Leader:	Hina Mehta, Pharm.D.

1 REASON FOR REVIEW

Versatem submitted a New Drug Application (NDA) 211155 for Copiktra (duvelisib) capsules on February 02, 2018. The Applicant is requesting a priority review for Copiktra indicated for the treatment of:

1) Chronic lymphocytic leukemia (CLL)/small lymphyocytic lymphoma (SLL), (b) (4) (b) (4)
2) Follicular B-cell non-Hodgkin lymphoma (FL) who have received at least two prior therapies

The Division of Hematology Products (DHP) requested DMEPA to review the Prescribing Information (PI), Medication Guide, and carton and container labeling of the product for areas of vulnerability that may lead to medication error.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material 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
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

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 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA evaluated the submitted PI, Medication Guide, and carton and container labeling for areas of vulnerability in regards to medication error. Our review identified areas in the labels and labeling that can be improved to increase readability and prominence of important information.

We provide our recommendations in Sections 4.1 and 4.2 and recommend their implementation prior to approval of this application.

4 CONCLUSION & RECOMMENDATIONS

We identified areas on the PI and container label that can be improved to increase clarity and prominence of important information to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights of Prescribing Information

1. Dosage and Administration

a. Consider adding a bullet stating "Make dose modifications based on adverse reactions (2.2, 2.3)". We recommend this as some of the strengths available are due to the dosage reductions.

B. Prescribing Information

1. Dosage and Administration Section
   a. We recommend combining section 2.1 (b) (4) and section 2.2 (b) (4). The heading can be revised to read "2.1 Dosing".

2. How Supplied/Storage and Handling Section
   a. We recommend revising the storage temperature to USP control temperature. Revise to "Store at 20° to 25°C (68° to 77°F), with excursions permitted at 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]."

4.2 RECOMMENDATIONS FOR VERSATEM

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

A. Blister Carton and Blister Pack Container

1. We recommend revising the storage temperature to USP control temperature: 20° to 25°C (68° to 77°F), with excursions permitted at 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]].
2. We recommend increasing the prominence of the "mg" next to the strength presentations (i.e. 25 mg, 15 mg, (b) (4)) in all the labels and labeling. Consider bolding the "mg" to align with strength information so it is not overlooked or confused with the net quantity.
3. We recommend adding the statement "Dispense the enclosed Medication Guide to each patient" or similar statement prominently displayed on the PDP per 21 CFR 208.24(d) to blister carton.
4. The linear drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to each blister packer and outer sleeve as required per 21CFR 201.25(c)(2).

5. The container blister pack label of 28 units and the carton labeling of 56 units should have different NDC numbers. Revise the NDC numbers so that the blister carton labeling and blister pack label NDC numbers are different for these two package configurations.

B. Container Label

1. See A.1 and A.2.
2. We recommend adding the statement "Dispense the enclosed Medication Guide to each patient" or similar statement prominently displayed on the PDP per 21 CFR 208.24(d).
3. We recommend you consider relocating the net quantity statement away from the product strength, such as to the bottom of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.
4. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to each container as required per 21CFR 201.25(c)(2).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Copiktra received on February 05, 2018, and March 22, 2018 from Verastem.

Table 2. Relevant Product Information for Copiktra	
Initial Approval Date	N/A
Active Ingredient	duvelisib
Indication	1) Chronic lymphocytic leukemia (CLL)/small lymphyocytic lymphoma (SLL), (b) (4) (b) (4) 2) Follicular B-cell nonh-Hodgkin lymphoma (FL) who have received at least two prior therapies
Route of Administration	Oral
Dosage Form	Capsules
Strength	(b) (4) 15 mg, 25 mg
Dose and Frequency	25 mg twice daily (dosage reductions to (b) (4) 15 mg twice daily based on adverse reactions)
How Supplied	Bottles of 56 count: (b) (4) 15 mg, and 25 mg
Storage	15° to 30°C (59° to 86°F) Retain in original package

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 01, 2018, we searched DMEPA's previous reviews using the terms, Copiktra. Our search did not identify any previous labeling reviews.

APPENDIX G.

LABELS AND LABELING

G.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 Copiktra labels and labeling submitted by Versatem.

- Container label received on February 05, 2018
- Blister Pack (28 capsules) labels received on February 05, 2018
- Medication Guide received on February 05, 2018
- Prescribing Information (Image not shown) received on February 05, 2018, and March 22, 2018

G.2 Label and Labeling Images

Container Labels: Bottles: (b) (4) 15 mg, 25 mg

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

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/s/

LEEZA RAHIMI
06/12/2018

HINA S MEHTA
06/12/2018

CLINICAL INSPECTION SUMMARY

Date	June 11, 2018
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Susan D. Thompson, M.D., GCPAB Team Leader, for Janice Pohlman M.D., M.P.H., GCPAB Team Leader Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Nicholas Richardson, D.O., M.P.H., Medical Officer Yvette Kasamon, M.D., Clinical Team Leader Rachel McMullen, M.P.H., M.H.A., Regulatory Project Manager Division of Hematology Products
NDA	211155 (IND 112486)
Applicant	Verastem, Inc.
Drug	duvelisib (IPI-145)
NME	Yes
Therapeutic Classification/Status	phosphoinositide-3-kinase (PI3K)-δ,γ inhibitor
Proposed Indication	(1) Treatment of thrombocytopenia in patients with treatment of follicular B-cell non-Hodgkin lymphoma (2) Treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma
Consultation Request Date	March 6, 2018
Summary Goal Date	August 1, 2018
Action Goal Date	October 5, 2018
PDUFA Date	October 5, 2018

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Flinn and Lunin) were selected by the Division of Hematology Products (DHP) for inspection in support of NDA 211155. The sponsor (Verastem, Inc.) was also inspected. 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 regulatory classification for Drs. Flinn and Lunin is No Action Indicated. The regulatory classification for the sponsor is No Action Indicated.

2. BACKGROUND

IPI-145 is a potent phosphoinositide-3-kinase (PI3K)-δ,γ inhibitor. PI3K-δ and PI3K-γ isoforms are necessary for adaptive and innate immunity, and are important mediators in inflammatory disorders and hematologic malignancies such as subsets of indolent non-Hodgkin lymphoma, chronic lymphocytic leukemia or small lymphocytic lymphoma.

Study IPI-145-06 was submitted for the following drug indication: treatment of follicular B-cell non-Hodgkin lymphoma who received at least two prior therapies.

Study IPI-145-07 was submitted for the following drug indication: treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma, (b) (4) (b) (4).

Study IPI-145-06:

Study IPI-145-06 was a Phase 2 open-label, single-arm efficacy and safety study of duvelisib administered orally to subjects with indolent non-Hodgkin lymphoma (iNHL, including follicular lymphoma, small lymphocytic lymphoma, or marginal zone lymphoma) whose disease is refractory to rituximab and to either chemotherapy or radioimmunotherapy (RIT). Subjects received a dose of 25 mg duvelisib twice daily over the course of 28-day treatment cycles until disease progression or unacceptable toxicity. The primary study objective was to evaluate the antitumor activity of duvelisib administered to subjects diagnosed with iNHL whose disease is refractory to rituximab and to either chemotherapy or RIT.

The primary study endpoint was overall response (ORR), with overall response defined as best response of complete response (CR) or partial response (PR) according to the revised International Working Group (IWG) Criteria. Response and progression status were evaluated locally (i.e., Investigator's assessment) and by an independent, third-party panel of radiologists and oncologists (Independent Review Committee [IRC]) according to the revised IWG Response Criteria. The IRC assessment was used for overall response.

This multicenter, multinational study enrolled subjects at 56 sites across 12 countries (including the U.S., Europe, and Canada). In total, 129 subjects received duvelisib during the study. The first subject enrolled on June 24, 2013. The data cutoff date for this report was April 7, 2016. There are 35 subjects remaining on duvelisib as of the April 7, 2016 cutoff date.

Study IPI-145-07

Study IPI-145-07 is a Phase 3 multicenter, 2-arm, randomized (1:1 ratio), open-label, parallel, Phase 3, superiority trial designed to evaluate the efficacy and safety of duvelisib monotherapy compared to ofatumumab monotherapy in subjects with relapsed/refractory chronic lymphocytic lymphoma or small lymphocytic lymphoma (CLL/SLL) who had previously received at least one anticancer therapy. The primary study objective was to examine the efficacy of duvelisib monotherapy versus ofatumumab monotherapy in subjects with relapsed or refractory CLL/SLL.

The primary efficacy endpoint was progression-free survival (PFS), defined as time from randomization to the first documentation of progressive disease (PD) as determined by independent review or death due to any cause.

This multicenter, multinational study enrolled subjects at 62 sites across 11 countries (including the U.S. and Europe). The Intent-To-Treat (ITT) analysis set is comprised of 319 study subjects (n = 160 duvelisib; n = 159 ofatumumab). The first subject enrolled on January 21, 2014. The data cutoff for this report was on May 19, 2017. As of May 19, 2017, 34 subjects remain on duvelisib and no subjects remain on ofatumumab.

3. RESULTS (by site):

Name of Clinical Investigator/Sponsor Address	**Protocol #/ Site #/# Subjects Enrolled**	**Inspection Dates**	**Classification**
Ian Flinn, M.D. 250 25th Avenue North, Suite 412 Nashville, TN 37203	Study: IPI-145-06 Site #001 6 subjects Study: IPI-145-07 Site #101 16 subjects	April 16 to 20, 2018	NAI
Scott Lunin, M.D. Address 1: 3840 Broadway Fort Myers, FL 33901	Study: IPI-145-06 Site #3 3 subjects Study: IPI-145-07 Site #117 9 subjects	March 26 to 29, 2018	NAI
Verastem, Inc. 117 Kendrick Street, Suite 500 Needham, MA 02494	Sponsor for: Study: IPI-145-06 Study: IPI-145-07	May 7 to 10, 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. Ian Flinn, MD

For Study IPI 145-06, a total of seven subjects were screened and six subjects were enrolled. No subjects completed study treatment: three patients died, one developed disease progression, and two subjects withdrew consent to further participate.

For Study IPI 145-07, a total of 16 subjects were screened and enrolled. Of the 11 subjects who discontinued while on treatment during the study, four withdrew consent, one subject developed disease progression, five subjects discontinued due to adverse events, and one subject died. Subsequently, five subjects completed treatment.

The inspection evaluated the following documents: paper and electronic source records, screening and enrollment logs, case report forms, adverse events, study drug accountability logs, study monitoring visits, training records, financial disclosure documents, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for three enrolled subjects in Study IPI 145-06 and for eight enrolled subjects in Study IPI 145-07, whose records were reviewed, were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. 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. Scott Lunin, M.D.

For Study IPI 145-06, a total of nine subjects were screened and three subjects were enrolled. One subject was removed from the study, and thus did not complete treatment. Two subjects completed treatment.

For Study IPI 145-07, a total of 13 subjects were screened and 9 subjects were enrolled. Three subjects withdrew from the study. Of the six that remained: five subjects completed treatment and one subject remains on study.

The inspection evaluated the following documents: source records, screening and enrollment logs, 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 nine screened subjects in Study IPI 145-06 and for 13 screened subjects in Study IPI 145-07, whose records were reviewed, were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. 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.

Sponsor

3. Verastem, Inc.

Records reviewed included but were not limited to: organizational charts; vendor list; vendor oversight plans; transfer of obligations; investigator agreements; financial disclosures; monitoring plans; monitoring reports; safety reports; adverse events; protocol deviations; and standard operating procedures. A total of 12 clinical sites in both studies were selected from the investigator listings for review of monitoring reports and monitor qualifications.

Monitoring reports indicated that the sites received adequate periodic monitoring. There was no under-reporting of serious adverse events by sponsor. In general, this sponsor appeared to be in compliance with Good Clinical Practice. No Form FDA 483 was issued.

{See appended electronic signature page}

Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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/s/

ANTHONY J ORENCIA
06/11/2018

SUSAN D THOMPSON
06/11/2018

Interdisciplinary Review Team for QT Studies Consultation: QT Study Review

IND or NDA	NDA 211155
Brand Name	COPIKTRA
Generic Name	Duvelisib
Sponsor	Verastem Inc.
Indication	Treatment of patients with CLL/SLL (b) (4) (b) (4) (b) (4) / Treatment of patients with FL who have received at least two prior therapies
Dosage Form	Capsules
Drug Class	PI3K-δ,γ
Therapeutic Dosing Regimen	25 mg BID
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	75 mg BID
Submission Number and Date	SDN 001; 5 Feb 2018
Review Division	DHP

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

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No large QTc prolongation effect (i.e., >20 ms) of duvelisib (25 and 75 mg BID) was detected in this QT study.

The effect of duvelisib was evaluated in a phase 1, open-label, dose escalation, maximum tolerated dose finding study in patients with advanced hematologic malignancies, which included two dose expansion cohorts (25 and 75 mg BID). A total of 210 patients received duvelisib (8 mg to 100 mg) in dose escalation and dose expansion phases of the study. Most of the data came from two expansion phase cohorts - duvelisib 25 mg BID (the proposed therapeutic dose) and duvelisib 75 mg BID (the maximum tolerated dose). The data from both the escalation and expansion phases were pooled and analyzed using exposure-response analysis, which suggests that duvelisib is not associated with large mean increases in the QTc interval (section 5.3) and an absence of dose-response for QTc. The findings of this analysis are further supported by available preclinical results (hERG assay and monkey CV safety study) (section 3.3) and by-time analysis of the 25 and 75 mg BID dose groups (section 5.2.1.1).

The highest dose studied (75 mg BID) produces mean C_{max} values of ~2-fold higher than the mean C_{max} for the therapeutic dose (25 mg BID). These concentrations are above those for the predicted worst case scenario (drug interaction with ketoconazole). It is expected from drug interaction studies that co-administration of duvelisib with ketoconazole can elevate duvelisib's mean C_{max} as much as 1.7-fold higher than the C_{max} of the 25 mg BID dose.

1.2 COMMENTS FOR THE REVIEW DIVISION

Increases in the PR interval were observed in study IPI-145-02. There were 16 (8%) subjects with PR values > 220 ms and 1 subject reported an adverse event (AE) of atrioventricular block, first degree. The maximum mean increase in the PR interval was 10 ms (UCL: 15 ms) in the 25 mg BID dose group. However, the increase in the PR interval was not dose-related as the largest mean increase was lower (5 ms) in the 75 mg BID group. Because of the lack in dose-response and the low incidence of AEs related to PR prolongation, we are not recommending that PR prolongation is included in the label unless the Review Division has additional information about AEs related to PR prolongation in other clinical trials.

1.3 RESPONSES TO QUESTIONS POSED BY REVIEW DIVISION

Division: The Division is requesting a QT-IRT review to verify the QT analysis and the accuracy of the labeling language. Do the data in the QT studies support the labeling language?

QT-IRT's response: No, we do not agree with the proposed labeling language from the sponsor. The study data submitted only supports excluding large mean increases in the QTc interval (i.e. 20 ms) at 25 and 75 mg BID dose levels, because the study did not include a negative or positive-control. This is acceptable as the indication sought is an oncology indication, however, because of this limitation we are proposing that the label states clearly which dose levels were the primary dose levels in the study (b) (4) (b) (4).

2 PROPOSED LABEL

The following are the sponsor's proposed labeling language related to QT:

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of multiple doses of COPIKTRA (b) (4) on the QTc interval was evaluated in patients with previously treated hematologic malignancies. (b) (4) (b) (4)

The following is QT-IRT's proposed labeling language, which is a suggestion only. We defer final labeling decisions to the Division. Of note, we are proposing only to include description of 25 and 75 mg dose levels as these were the main dose groups in the study. Lastly, as the study was designed to exclude large mean increases it is not appropriate to note that no relationship between COPIKTRA exposure and changes in the QTc interval was observed.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of multiple doses of COPIKTRA 25 and 75 mg twice daily on the QTc interval was evaluated in patients with previously treated hematologic malignancies, which showed an absence of large mean increases in the QTc interval.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Duvelisb (IPI-145) is an oral, dual inhibitor of phosphoinositide-3-kinase (PI3K)-δ and PI3K-γ within the pharmacological class of kinase inhibitors.

3.2 MARKET APPROVAL STATUS

Duvelisb is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

In safety pharmacology studies, duvelisib and its primary metabolite (IPI-656) inhibited the hERG potassium current with IC50 values of 49.8 μM and > 100 μM, respectively, indicating a very low potential for cardiac repolarization (QT) prolongation in humans. The duvelisib IC50 for hERG inhibition is 1060-fold greater than the expected free concentration of duvelisib in patients at the intended commercial dose (25 mg BID), and the hERG IC50 for IPI-656 is estimated to be greater than 2600-fold above the proposed clinical free Cmax of the metabolite.

In monkeys, no duvelisib-related effects were observed on hemodynamic or electrocardiographic parameters, heart rate, or quantitative electrocardiographic intervals following a single oral dose up to 150 mg/kg. In addition, no waveform abnormalities or arrhythmias related to the administration of duvelisib were noted at any dose level.

3.4 CLINICAL EXPERIENCE

Electrocardiogram data were analyzed for the integrated safety dataset. Less than 1.5% of subjects had a Fridericia's corrected QT interval (QTcF) > 500 msec and change from Baseline in QTcF ≥60 msec (Study VS2700006A). Additionally, across all studies there were few clinically significant electrocardiogram (ECG) abnormalities reported, and no trends were observed in these abnormalities.

In the duvelisib data base 4 subjects had Adverse Events (AEs) of Electrocardiogram QT Prolonged. Review of ECG intervals from these subjects showed, however, that only 2 of 4 had QTcF prolongation (QTcF>450 msec); and both of them had prolongation before receiving any duvelisib. A 5th subject was of interest because she had an AE of ventricular tachycardia, but available documentation did not show that this AE was related to QT prolongation. Clinical experience linking duvelisib with QT prolongation is minimal or non-existent.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of duvelisib's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT did not review the protocol prior to conducting this study. The sponsor requested feedback on the proposed strategy for QT in 2015, where the QT-IRT advised the sponsor that the data appears to support excluding large mean increases in the QT interval (DARRTS 02/23/2015). Later in 2017, the sponsor requested advice on a new proposal, and the QT-IRT again advised that the data described would be adequate to exclude large mean increases (particularly study IPI-145-02) and that we did not agree with (b) (4).

The sponsor submitted clinical study report (for study IPI-145-02) as well as two concentration-QTc analysis reports VS27000006A and (b) (4). The VS27000006A report and data sets from study IPI-145-02 will be the focus of this review.

In addition, the electronic datasets were submitted and waveforms were uploaded to the ECG warehouse.

4.2 CONCENTRATION QT REPORT

4.2.1 Title

Population Duvelisib Exposure-dQTc Analysis

4.2.2 Protocol Number

VS27000006AIPI-145-02

4.2.3 Study Dates

First subject enrolled: 27 October 2011

Cutoff for CSR: 27 February 2015

4.2.4 Objectives

The objective of the duvelisib exposure-response analysis was to characterize the relationship between change from baseline QTc (dQTc) and duvelisib and IPI-656 exposure in patients with hematologic malignancies from Study IPI-145-02.

4.2.5 Study Description

4.2.5.1 Design

This concentration-QTc report includes data from one study (IPI-145-02). IPI-145-02 is a phase 1, open-label, dose-escalation study followed by an expansion phase in patients with advanced hematologic malignancies.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Duvelisib was administered orally (as capsules) twice daily within 28-day cycles in all parts of the study. Dose levels examined during the Dose Escalation Phase were based on 3+3 design and are presented in Table 10.

Table 10: Dose Escalation Dose Levels

	Accelerated Phase		Standard Phase					
Duvelisib dose (BID)	**8 mg** N = 1	**15 mg** N = 6	**25 mg** N = 7	**35 mg** N = 3	**50 mg** N = 3	**60 mg** N = 4	**75 mg** N = 6	**100 mg** N = 3

During the Dose Escalation Phase, an Expansion Cohort at 25 mg BID was opened in select hematologic malignancies based on the observed efficacy and safety. Fifty-nine subjects were treated in the 25 mg BID Expansion Cohorts. Following determination of the MTD at 75 mg BID, Expansion Cohorts in select hematologic malignancies were opened at 75 mg BID. One hundred and eighteen subjects were treated in the 75 mg BID Expansion Cohorts.

Table 11: Dose Expansion Dose Levels

	Expansion Phase	
Duvelisib dose (BID)	**25 mg** N = 59	**75 mg** N = 118

4.2.6.2 Sponsor's Justification for Doses

The initial dose included in the expansion phase was 25 mg BID, based on observed efficacy and safety. Following determination of the MTD dose (75 mg BID) an additional expansion cohort of 75 mg BID was added. The proposed dose in the label is 25 mg BID.

Reviewer's Comment: Acceptable.

4.2.6.3 Instructions with Regard to Meals

Drug was administered without regard to food.

Reviewer's Comment: Acceptable. High-fat meals delay absorption (T_{max} is delayed from 1 to 4 h) with a minimal impact on C_{max} (decrease by ~37%) and no significant effect on AUC.

4.2.6.4 ECG and PK Assessments

ECG/PK collection in day 1 in cycles 1 and 2: predose, 1, 2, 4, 6 and 8 h post-dose

Reviewer's Comment: Acceptable, covers the anticipated T_{max} (1-4 h) and allows for detection of delayed effects.

4.2.6.5 Baseline

The average of predose QT/QTc values on Cycle 1 Day 1 was used as baseline.

4.2.7 ECG Collection

Standard 12-Lead ECGs were collected in triplicates while subjects were in semi-recumbent or supine position.

4.2.8 Sponsor's Results

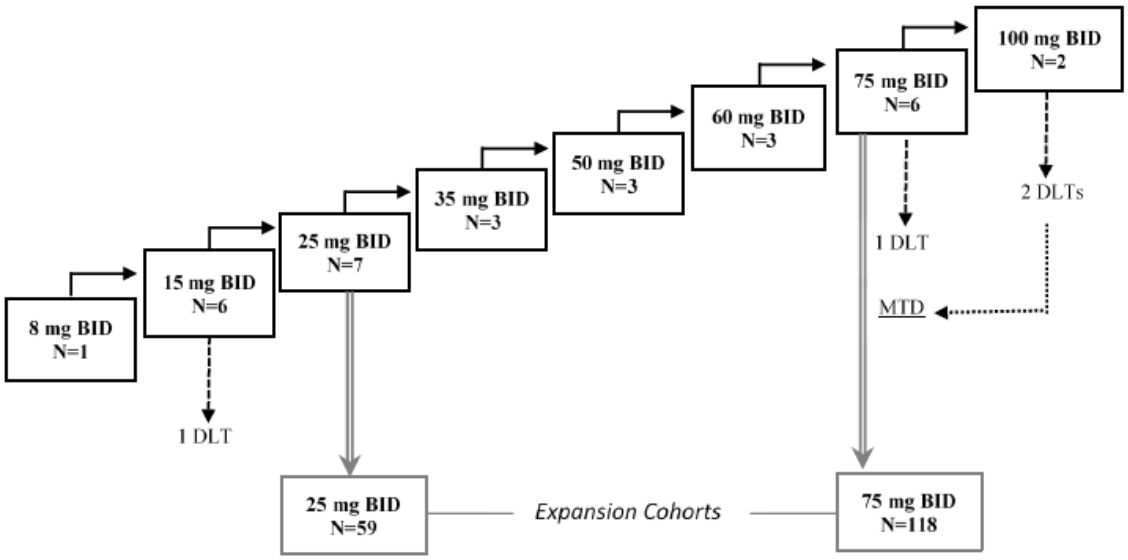
4.2.8.1 Study Subjects

A total of 210 patients (78 females and 132 males) with hematologic malignancies received duvelisib in the study (All-treated Analysis Set). Two patients (SUBJID (b) (6) and (b) (6)) were not included in exposure-response analysis due to no predose records.

The average age (SD) of the 210 patients was 64.0 (12.1) years, ranging from 25 to 86 years. Overall, 116 patients (116/210, 55.2%) were ≥65 years old, while the remaining 94 patients (94/210, 44.8%) were <65 years. Most patients were White (185/210, 88.1%), and 18 patients (18/210, 8.6%) were Black or African American.

The following figure displays number of patients in each dose escalation and expansion cohort.

Figure 1: Subject Enrollment (Dose Escalation and Expansion Cohorts)



*Note: Two additional subjects received duvelisib in DE (one assigned to 60 mg BID and the other to 100 mg BID), but were not included in the DES since they did not experience a DLT and did not receive ≥ 75% of their assigned Cycle 1 doses.

Source: IPI-145-02 clinical study report, *Figure 2, page 78*

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

Exposure-response analysis was used for primary analysis. The findings of the study are discussed in section 4.2.8.4.

4.2.8.2.2 Assay Sensitivity

Not Applicable

4.2.8.2.3 Categorical Analysis

Overall, a total of 3 patients contributed 14 records with dQTcP ≥60 msec. Of the 3 patients, two patients (SUBJID (b) (6) (n=10) and SUBJID (b) (6) (n=1)) were from the 25 mg b.i.d dose group and one from the 75 mg b.i.d dose group (SUBJID (b) (6) (n=3)). SUBJID (b) (6) had a low baseline QTcP (at pre-dose (Day 1)) of 371 msec compared to screening and post-dose QTcP values (range: 421-474) msec that contributed towards the very high dQTcP values for this patient. In the IPI-656 dataset, following 25 mg b.i.d. dose, there were no observation records with dQTcP ≥60 msec.

In the present analysis dataset, less than 1%, 1.4% amd 20% patients had QTcF>500 msec, QTcF>480 msec and QTcF>480 msec, respectively. Correspondingly, less than 1%, 2.4% amd 22% patients had QTcP>500 msec, QTcP>480 msec and QTcP>480 msec, respectively. Also, only 1.4% and 10% patients had dQTcF>60 msec and dQTcF>30 msec, respectively. Similarly, only 1.4% and 9.6% patients had dQTcP>60 msec and dQTcP>30 msec, respectively.

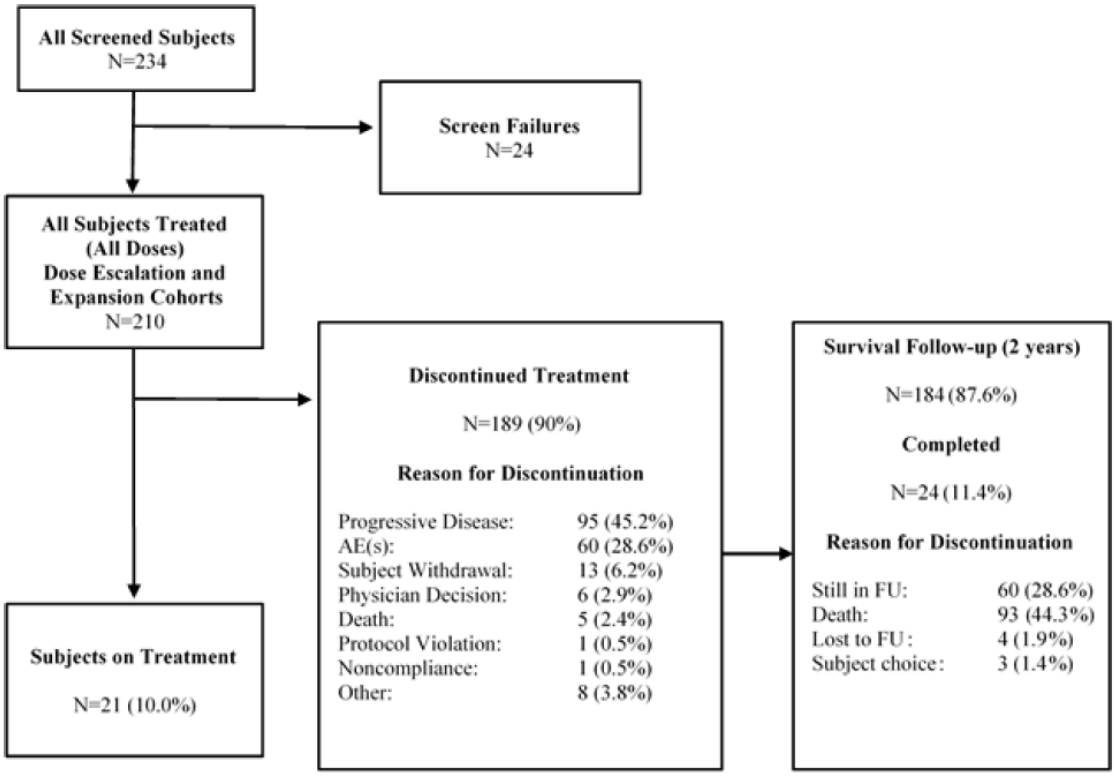
Reviewer's comment: The second QTcX > 480 ms should probably be 450 ms.

4.2.8.3 Safety Analysis

The subject disposition flowchart in Figure 2 displays the safety profile of duvelisib.

There were no clinically significant ECG findings in the overall study population.

Figure 2: Subject Disposition
(All Subjects, Dose Escalation and Expansion Cohorts)



Source: IPI-145-02 clinical study report, *Figure 3, page 79*

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 1, which shows approximately ~2-fold higher C_{max} at steady-state for 75 mg BID (MTD) compared to 25 mg BID (maximum proposed therapeutic dose).

Table 1: C_{max} by visit, dose and analyte

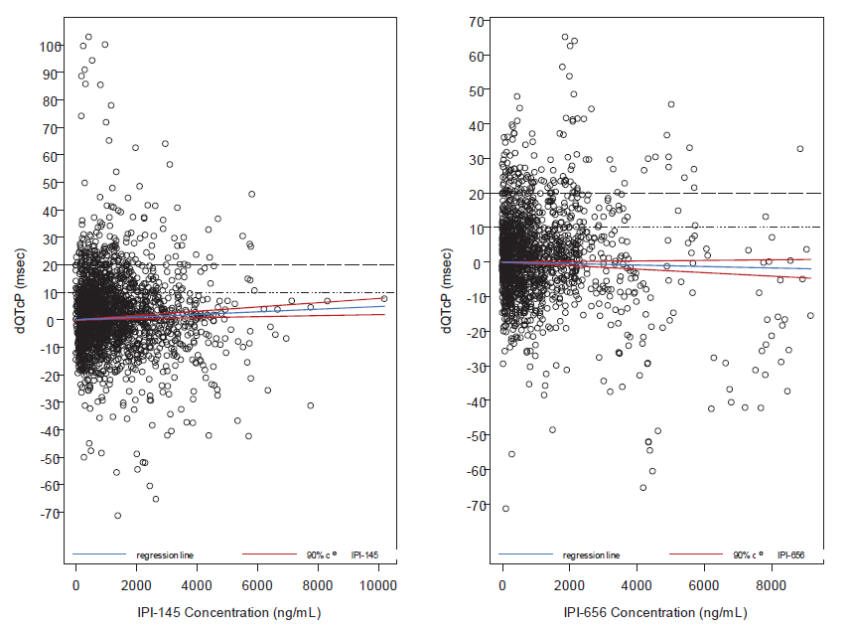
Visit	Dose	Duvelisib	IPI-656
Cycle 1, Day 1			
	25 mg BID	1062 ng/mL	227.1 ng/mL
	75 mg BID	2630 ng/mL	740.2 ng/mL
Cycle 2, Day 1			
	25 mg BID	1511 ng/mL	1333 ng/mL
	75 mg BID	3294 ng/mL	2568 ng/mL

Source: Pharmacokinetic / Pharmacodynamic report for IPI-145-02, *Tables 6,7, 9,10*

4.2.8.4.2 Exposure-Response Analysis

Calculation and Exploratory Review of the Observed dQTcP Data

Using the estimated population CF, population-corrected baseline QTcP (QTcPbaseline), QTcP at each post-dose sampling time and the change from baseline QTcP (dQTcP) were calculated for each patient. Linear regression lines for the observed dQTcP versus duvelisib and IPI-656 concentrations for all data displayed in Summary Figure 1 suggested a positive relationship (SLP>0) between duvelisib concentrations and dQTcP but no relationship (SLP~0) between IPI-656 concentrations and dQTcP.



Assessment of Hysteresis

Mean dQTcP versus mean duvelisib and IPI-656 concentration plots and the individual plots of dQTcP versus duvelisib and IPI-656 concentration indicated that there was no evidence of hysteresis. Although the peak for dQTcP occurred slightly later than the peak for duvelisib, it occurred around the same time as the peak of IPI-656 indicating no evidence of hysteresis.

Exposure-dQTcP Final Models

Linear models with SLP and INT terms were considered as final models for duvelisib (QT145013d) and IPI-656 (Run QT656013d) (Summary Table 1 and Summary Table 2). The typical estimates of duvelisib and IPI-656 SLP were 0.698 (0.0336, 1.36) and 1.44

(0.156, 2.72) msec/(μg/mL) and were estimated with reasonable precision (RSE<50%). The typical estimate of duvelisib and IPI-656 INT was fixed to 0.

The estimated mean (95% CI) slope parameter values show that higher duvelisib and IPI-656 concentrations were associated with higher dQTcP. The maximum increase in dQTcP in patients corresponding to maximum observed duvelisib concentration in the dataset (10.2 μg/mL observed at 75 mg b.i.d.) would be 7.12 (95% CI: 0.343, 13.9) msec. The maximum increase in dQTcP in patients corresponding to maximum observed IPI-656 concentration in the dataset (9.17 μg/mL observed at 75 mg b.i.d.) would be 13.2 (95% CI: 1.43, 24.9) msec. The median concentrations across all doses (8 to 100 mg b.i.d.) for duvelisib and IPI-656 were 914 and 692 ng/mL, respectively.

Further, as an extension of the final duvelisib exposure-dQTcP model, separate SLP terms were estimated for 25 mg and 75 mg b.i.d. dose groups. The typical estimate of SLP for 25 mg b.i.d.dose was estimated with a reasonable precision (RSE=49.5%) but the typical estimate of SLP for 75 mg b.i.d. dose was estimated with poor precision (RSE=276%). The typical estimate (95% CI) of SLP for 75 mg b.i.d. dose was lower [0.216 (95% CI: -0.954, 1.39) msec/(μg/mL)] compared to the 25 mg b.i.d. dose [2.81 (95% CI: 0.0856, 5.53) msec/(μg/mL)].

Also, as an extension of the final IPI-656 exposure-dQTcP model, separate SLP terms were estimated for 25 mg and 75 mg b.i.d. dose groups. The typical SLP for 25 mg b.i.d. dose was estimated with a reasonable precision (RSE=33.3%) but the typical SLP for 75 mg b.i.d. dose was estimated with low precision (RSE=78.1%). The typical estimate (95% CI) of SLP for 75 mg b.i.d. dose was lower [1.00 (95% CI: -0.531, 2.53) msec/(μg/mL)] compared to the 25 mg b.i.d. dose [4.29 (95% CI: 1.49, 7.09) msec/(μg/mL)].

Reviewer's Analysis: The results of the reviewer's analysis is shown in section 5.3, which is similar to the sponsor's analysis and suggests an absence of large mean increases in the QTc interval.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcP for their primary analysis, which was derived based on the pooled screening and baseline ECGs. Since no large changes in heart rate were observed, i.e., mean changes ≤10 bpm (section 5.2.2), no assessment of the QT/RR correction methodology is necessary and QTcF is used for all reviewers' assessments, which resulted in results comparable to the sponsor's analysis using QTcP.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Duvelisib

The statistical reviewer listed descriptive statistics of QTcF and used mixed model to analyze the ΔQTcF effect by treatment and cycle. The model includes time effect, and

baseline values are also included in the model as a covariate. The analysis results are listed in the following table.

Table 2: Analysis Results of QTcF and ΔQTcF

				QTcF (ms)		ΔQTcF (ms)			
Cycle	**Treatment**	**Day**	**Time (Hour)**	**N**	**Mean (SE)**	**N**	**LSMean**	**SE**	**90% CI**
1	Duvelisib 25 mg BID	1	1	63	419.9 (2.9)	63	3.5	1.7	(0.6, 6.3)
			2	65	422.4 (2.8)	65	5.3	1.7	(2.5, 8.1)
			4	65	419.8 (2.6)	65	2.7	1.4	(0.3, 5.0)
			6	65	416.4 (2.7)	65	-0.6	1.8	(-3.7, 2.4)
			8	64	417.1 (2.6)	64	0.1	1.6	(-2.5, 2.7)
	Duvelisib 75 mg BID	1	1	123	419.0 (2.1)	123	1.1	0.8	(-0.1, 2.4)
			2	123	419.7 (2.1)	123	1.9	1.0	(0.3, 3.6)
			4	121	420.8 (2.0)	121	2.8	1.0	(1.1, 4.5)
			6	122	417.2 (1.8)	122	-0.8	1.1	(-2.6, 0.9)
			8	121	417.8 (1.9)	121	-0.7	1.2	(-2.7, 1.3)
2	Duvelisib 25 mg BID	1	0	54	421.7 (2.9)	54	5.9	2.2	(2.2, 9.7)
			1	54	424.5 (3.0)	54	8.7	2.1	(5.2, 12.2)
			2	54	427.2 (3.0)	54	11.4	2.5	(7.2, 15.6)
			4	54	424.2 (2.7)	54	8.5	2.1	(4.9, 12.0)
			6	54	419.1 (2.7)	54	3.3	2.2	(-0.4, 7.0)
			8	54	419.5 (2.9)	54	3.7	2.3	(-0.1, 7.6)
	Duvelisib 75 mg BID	1	0	99	420.3 (2.0)	99	2.2	1.4	(-0.1, 4.5)
			1	99	423.1 (2.1)	99	4.4	1.4	(2.1, 6.8)
			2	99	423.0 (2.1)	99	5.2	1.4	(2.8, 7.6)
			4	99	423.8 (2.2)	99	5.5	1.5	(2.9, 8.1)
			6	100	418.1 (2.1)	100	-0.5	1.5	(-2.9, 2.0)
			8	98	417.6 (2.1)	98	-0.7	1.5	(-3.2, 1.7)

On Cycle 1 Day 1 (single dose), the largest upper bounds of the 2-sided 90% CI for the mean change from baseline in QTcF (ΔQTcF) were 8.1 ms and 4.5 ms for duvelisib 25 mg BID and duvelisib 75 mg BID, respectively. On Cycle 2 Day 1 (multiple doses), the largest upper bounds of the 2-sided 90% CI for ΔQTcF were 15.6 ms and 8.1 ms for duvelisib 25 mg BID and duvelisib 75 mg BID, respectively.

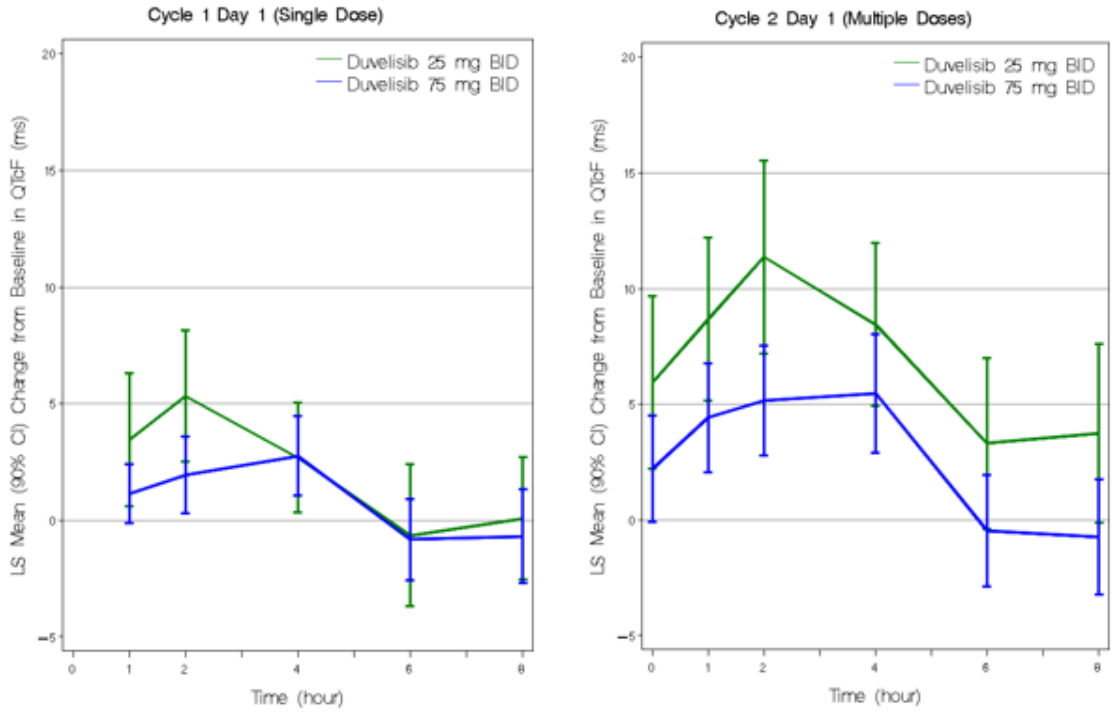
5.2.1.2 Assay Sensitivity Analysis

No placebo or positive control was used in the study.

5.2.1.3 Graph of ΔQTcF Over Time

The following figure displays the time profile of ΔQTcF for different treatment groups.

Figure 3: Mean and 90% CI ΔQTcF Timecourse



5.2.1.4 Categorical Analysis

Table 3 lists the number of subjects as well as the number of observations whose QTcF values were ≤ 450 ms, between 450 ms and 480 ms, between 450 ms and 480 ms, and >500 ms.

Table 3: Categorical Analysis for QTcF

	Total N		450<QTcF<=480 ms		480<QTcF<= 500 ms		QTcF>500 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Baseline (All Dose Levels Pooled)	210	210	12 (5.7%)	12 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Duvelisib 25 mg BID	66	657	17 (25.8%)	60 (9.1%)	2 (3.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
Duvelisib 75 mg BID	124	1209	21 (16.9%)	97 (8.0%)	0* (0.0%)	3 (0.2%)	1 (0.8%)	1 (0.1%)
All Dose Levels Pooled**	210	2058	39 (18.6%)	163 (7.9%)	2 (1.0%)	5 (0.2%)	1 (0.5%)	1 (0.0%)

* One subject had 1 observation with QTcF >500 ms and 3 observations with QTcF between 480 ms and 500 ms. The subject was categorized to QTcF >500 ms group.

**All dose levels (escalation and expansion)

Table 4 lists the categorical analysis results for ΔQTcF.

Table 4: Categorical Analysis of ΔQTcF

	Total N		30<ΔQTcF<=60 ms		ΔQTcF>60 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Duvelisib 25 mg BID	66	657	7 (10.6%)	13 (2.0%)	2 (3.0%)	11 (1.7%)
Duvelisib 75 mg BID	124	1209	11 (8.9%)	39 (3.2%)	1 (0.8%)	1 (0.1%)
All Dose Levels Pooled*	210	2058	18 (8.6%)	52 (2.5%)	3 (1.4%)	12 (0.6%)

*All dose levels (escalation and expansion)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 5. On Cycle 1 Day 1 (single dose), the largest upper bounds of the 2-sided 90% CI for the mean change from baseline in HR (ΔHR) were 4.3 bpm and 4.7 bpm for duvelisib 25 mg BID and duvelisib 75 mg BID, respectively. On Cycle 2 Day 1 (multiple doses), the largest upper bounds of the 2-sided 90% CI for ΔHR were 4.0 bpm and 3.6 bpm for duvelisib 25 mg BID and duvelisib 75 mg BID, respectively.

The outlier analysis results for HR are presented in Table 6.

Table 5: Analysis Results of HR and ΔHR

				HR (ms)		ΔHR (ms)			
Cycle	Treatment	Day	Time (Hour)	N	Mean (SE)	N	LSMean	SE	90% CI
1	Duvelisib 25 mg BID	1	1	63	67.2 (1.8)	63	-2.6	0.6	(-3.5, -1.6)
			2	65	67.8 (1.7)	65	-1.7	0.6	(-2.7, -0.6)
			4	65	69.8 (1.7)	65	0.3	0.8	(-1.0, 1.6)
			6	65	72.4 (1.5)	65	2.9	0.9	(1.5, 4.3)
			8	64	69.8 (1.5)	64	0.4	0.9	(-1.1, 1.9)
	Duvelisib 75 mg BID	1	1	123	70.8 (1.2)	123	-3.4	0.4	(-4.1, -2.8)
			2	123	71.5 (1.2)	123	-2.7	0.5	(-3.5, -2.0)
			4	121	73.9 (1.3)	121	-0.4	0.6	(-1.4, 0.7)
			6	122	77.8 (1.1)	122	3.5	0.7	(2.3, 4.7)
			8	121	75.6 (1.1)	121	1.5	0.7	(0.3, 2.6)
2	Duvelisib 25 mg BID	1	0	54	65.9 (1.7)	54	-3.5	0.8	(-4.9, -2.1)
			1	54	63.7 (1.7)	54	-5.6	0.9	(-7.1, -4.2)
			2	54	64.3 (1.8)	54	-5.0	0.9	(-6.6, -3.5)
			4	54	67.0 (1.8)	54	-2.4	1.2	(-4.4, -0.4)
			6	54	71.0 (1.7)	54	1.6	1.4	(-0.8, 4.0)
			8	54	69.3 (1.7)	54	-0.1	1.2	(-2.1, 2.0)
	Duvelisib 75 mg BID	1	0	99	71.8 (1.3)	99	-1.6	0.9	(-3.1, -0.1)
			1	99	68.0 (1.2)	99	-5.3	0.9	(-6.8, -3.8)

				HR (ms)		ΔHR (ms)			
Cycle	Treatment	Day	Time (Hour)	N	Mean (SE)	N	LSMean	SE	90% CI
			2	99	68.9 (1.3)	99	-4.6	0.9	(-6.2, -3.1)
			4	99	71.5 (1.3)	99	-1.9	1.1	(-3.6, -0.1)
			6	100	75.5 (1.2)	100	2.0	0.9	(0.4, 3.6)
			8	98	75.0 (1.3)	98	1.6	1.1	(-0.2, 3.3)

Table 6: Categorical Analysis Results for HR

	Total N	HR<=100 bpm	HR>100 bpm	HR>45 bpm	HR<=45 bpm
Treatment Group	Subj. #	Subj. #	Subj. #	Subj. #	Subj. #
Baseline (All Dose Levels Pooled)	210	201 (95.7%)	9 (4.3%)	209 (99.5%)	1 (0.5%)
Duvelisib 25 mg BID	66	60 (90.9%)	6 (9.1%)	63 (95.5%)	3 (4.5%)
Duvelisib 75 mg BID	124	113 (91.1%)	11 (8.9%)	123 (99.2%)	1 (0.8%)
All Dose Levels Pooled*	210	190 (90.5%)	20 (9.5%)	206 (98.1%)	4 (1.9%)

*All dose levels (escalation and expansion)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 7. On Cycle 1 Day 1 (single dose), the largest upper bounds of the 2-sided 90% CI for the mean change from baseline in PR (ΔPR) were 9.8 ms and 3.7 ms for duvelisib 25 mg BID and duvelisib 75 mg BID, respectively. On Cycle 2 Day 1 (multiple doses), the largest upper bounds of the 2-sided 90% CI for ΔPR were 14.6 ms and 6.8 ms for duvelisib 25 mg BID and duvelisib 75 mg BID, respectively.

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

Table 7: Analysis Results of PR and ΔPR

				PR (ms)		ΔPR (ms)			
Cycle	Treatment	Day	Time (Hour)	N	Mean (SE)	N	LSMean	SE	90% CI
1	Duvelisib 25 mg BID	1	1	61	178.6 (4.6)	61	5.7	2.4	(1.6, 9.8)
			2	62	177.8 (4.4)	62	5.3	2.4	(1.3, 9.2)
			4	62	176.7 (3.8)	62	4.1	1.3	(1.9, 6.3)
			6	62	176.0 (3.7)	62	3.4	1.2	(1.4, 5.5)
			8	61	177.0 (3.8)	61	4.3	1.2	(2.3, 6.4)
	Duvelisib 75 mg BID	1	1	120	166.2 (2.2)	120	2.7	0.6	(1.6, 3.7)
			2	120	165.7 (2.2)	120	2.1	0.7	(1.0, 3.2)
			4	118	164.6 (2.2)	118	1.1	0.7	(-0.0, 2.3)

				PR (ms)		ΔPR (ms)			
Cycle	Treatment	Day	Time (Hour)	N	Mean (SE)	N	LSMean	SE	90% CI
			6	119	162.4 (2.1)	119	-1.3	0.8	(-2.6, 0.0)
			8	118	163.8 (2.1)	118	0.0	0.9	(-1.5, 1.5)
2	Duvelisib 25 mg BID	1	0	51	179.8 (3.8)	51	4.8	1.8	(1.9, 7.8)
			1	51	184.9 (4.0)	51	9.9	1.8	(6.9, 12.9)
			2	51	183.8 (5.0)	51	8.8	3.4	(3.1, 14.6)
			4	51	184.9 (4.3)	51	10.0	2.2	(6.3, 13.7)
			6	51	181.0 (3.8)	51	6.0	1.9	(2.9, 9.2)
			8	51	183.9 (4.3)	51	9.0	2.0	(5.6, 12.4)
	Duvelisib 75 mg BID	1	0	98	166.3 (2.2)	98	1.6	1.3	(-0.5, 3.8)
			1	98	168.9 (2.2)	98	4.3	1.2	(2.4, 6.2)
			2	98	168.9 (2.4)	98	4.5	1.3	(2.3, 6.8)
			4	98	166.9 (2.2)	98	2.4	1.2	(0.4, 4.5)
			6	100	165.7 (2.3)	100	1.4	1.3	(-0.6, 3.5)
			8	98	165.4 (2.2)	98	1.1	1.2	(-0.8, 3.1)

Table 8: Categorical Analysis for PR

	Total N		200<PR<=220 ms		PR>220 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline (All Dose Levels Pooled)	204	204	9 (4.4%)	9 (4.4%)	4 (2.0%)	4 (2.0%)
Duvelisib 25 mg BID	63	625	8 (12.7%)	79 (12.6%)	9 (14.3%)	53 (8.5%)
Duvelisib 75 mg BID	121	1190	14 (11.6%)	70 (5.9%)	6 (5.0%)	22 (1.8%)
All Dose Levels Pooled*	204	2007	23 (11.3%)	157 (7.8%)	16 (7.8%)	76 (3.8%)

*All dose levels (escalation and expansion)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 9. On Cycle 1 Day 1 (single dose), the largest upper bounds of the 2-sided 90% CI for the mean change from baseline in QRS (ΔQRS) were 1.9 ms and 1.6 ms for duvelisib 25 mg BID and duvelisib 75 mg BID, respectively. On Cycle 2 Day 1 (multiple doses), the largest upper bounds of the 2-sided 90% CI for ΔQRS were 4.1 ms and 3.1 ms for duvelisib 25 mg BID and duvelisib 75 mg BID, respectively.

The outlier analysis results for QRS are presented in Table 10.

Table 9: Analysis Results of QRS and ΔQRS

				QRS (ms)		ΔQRS (ms)			
Cycle	Treatment	Day	Time (Hour)	N	Mean (SE)	N	LSMean	SE	90% CI
1	Duvelisib 25 mg BID	1	1	64	100.3 (2.0)	64	1.0	0.5	(0.1, 1.8)
			2	65	100.0 (2.0)	65	0.8	0.6	(-0.2, 1.9)
			4	65	98.9 (2.0)	65	-0.3	0.7	(-1.4, 0.9)
			6	65	98.3 (1.9)	65	-0.8	0.9	(-2.3, 0.6)
			8	64	99.1 (1.9)	64	-0.0	0.8	(-1.4, 1.3)
	Duvelisib 75 mg BID	1	1	123	94.2 (1.3)	123	0.3	0.4	(-0.4, 0.9)
			2	123	94.7 (1.3)	123	0.8	0.5	(0.0, 1.6)
			4	121	94.2 (1.3)	121	0.4	0.5	(-0.5, 1.2)
			6	122	94.1 (1.3)	122	0.2	0.5	(-0.6, 1.0)
			8	121	93.9 (1.2)	121	-0.0	0.5	(-0.9, 0.8)
2	Duvelisib 25 mg BID	1	0	54	99.8 (2.1)	54	0.2	0.5	(-0.6, 1.1)
			1	54	99.6 (2.1)	54	0.0	0.4	(-0.7, 0.7)
			2	54	101.8 (2.3)	54	2.3	1.1	(0.4, 4.1)
			4	54	100.7 (2.2)	54	1.1	0.6	(0.1, 2.1)
			6	54	98.9 (2.2)	54	-0.7	1.1	(-2.4, 1.1)
			8	54	98.7 (2.1)	54	-0.9	0.8	(-2.2, 0.5)
	Duvelisib 75 mg BID	1	0	99	95.5 (1.3)	99	1.6	0.7	(0.5, 2.7)
			1	99	96.1 (1.3)	99	2.1	0.6	(1.1, 3.1)
			2	99	95.2 (1.3)	99	1.4	0.7	(0.2, 2.6)
			4	99	94.8 (1.2)	99	1.0	0.7	(-0.2, 2.1)
			6	100	94.4 (1.4)	100	0.1	0.7	(-1.0, 1.2)
			8	98	94.0 (1.3)	98	0.0	0.7	(-1.1, 1.1)

Table 10: Categorical Analysis for QRS

	Total N		QRS<=110 ms		QRS>110 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline (All Dose Levels Pooled)	210	210	190 (90.5%)	190 (90.5%)	20 (9.5%)	20 (9.5%)
Duvelisib 25 mg BID	66	658	50 (75.8%)	561 (85.3%)	16 (24.2%)	97 (14.7%)
Duvelisib 75 mg BID	124	1209	102 (82.3%)	1077 (89.1%)	22 (17.7%)	132 (10.9%)
All Dose Levels Pooled*	210	2059	171 (81.4%)	1829 (88.8%)	39 (18.6%)	230 (11.2%)

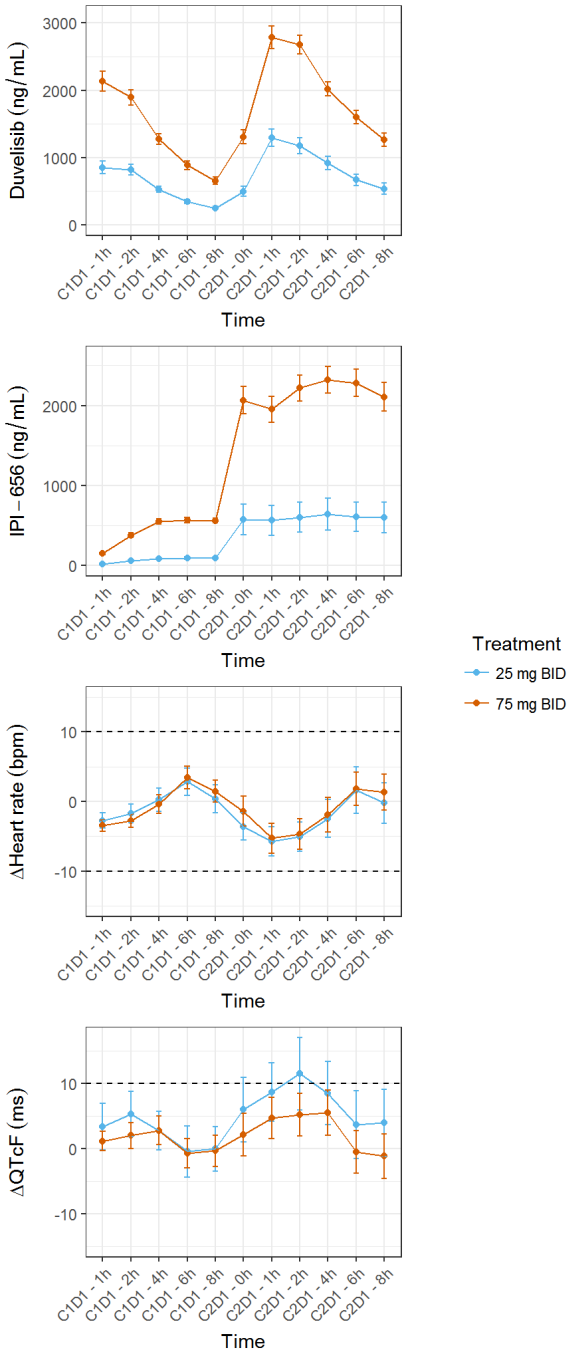
*All dose levels (escalation and expansion)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The objective of the clinical pharmacology analysis is to assess the relationship between duvelisib concentration and ΔQTcF.

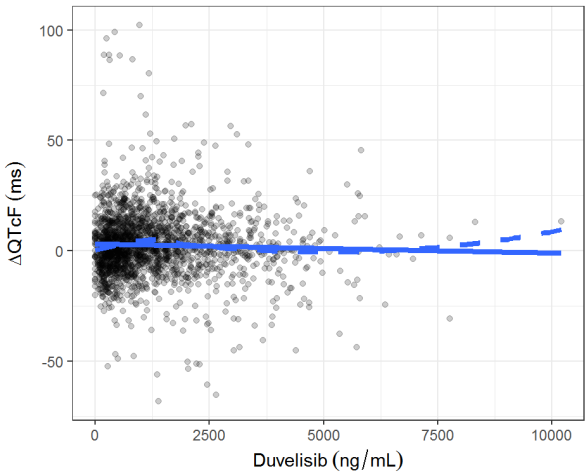
Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and ΔQTcF and 3) presence of non-linear relationship. An evaluation of the time-course of duvelisib pharmacokinetics and changes in ΔHR and ΔQTcF is shown in Figure 4, which shows an absence of significant changes in HR and do not appear to show significant hysteresis.

Figure 4: Time course of duvelisib concentration (top), heart rate (middle) and QTcF (bottom) cycle 1 day 1 and cycle 2 day 1



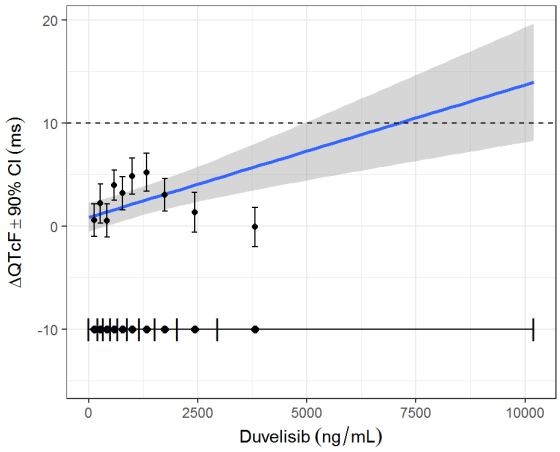
After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between duvelisib concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 5 shows the relationship between duvelisib concentration and ΔQTcF and supports the appropriateness of a linear model by study.

Figure 5: Assessment of linearity of concentration-QTc relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 6, which does not suggest the presence of a linear relationship to concentration or the presence of large mean increases (i.e. 20 ms). A similar conclusion was reached by the sponsor.

Figure 6: Goodness-of-fit plot for QTc



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

There were no adverse events of seizure, significant ventricular arrhythmias or sudden cardiac deaths that occurred in the study. Two subjects [redacted] (b) (6) reported non-serious syncope adverse events.

There were 4 subjects who had QTcF >500 ms or ΔQTcF >60 ms.

- Subject (b) (6) (75 mg dose BID) had a QTcF>500 ms on Cycle 2, day 1 and 3 additional values >480 ms. The subject's baseline was prolonged (QTcF was 465 ms) and none of the post-treatment QTcF values were >60 ms increase from baseline.
- Subject (b) (6) (25 mg dose BID) had change from baseline QTcF >60 ms for all post-treatment time points, although none of the QTcF values were >480 ms. These outlier values could have been caused by the low baseline value of 375 ms because the screening QTcF was 468 ms.
- Subject (b) (6) (25 mg BID) had QTcF >480 ms and increases from baseline QTcF >60 ms on Cycle 2, Day 1.
- Subject (b) (6) (75 mg BID) had at one time point a QTcF value of 434 ms which is an increase of 61 ms from baseline (373 ms).

5.4.2 ECG assessments

1323 paper ECGs were submitted and 6191 waveforms were uploaded to the ECG warehouse. Only 19 out of 210 subjects did not have digital ECGs in the ECG warehouse. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

No clinically relevant QRS prolongation was observed.

For the PR interval, there were increases in the PR interval, but the increase was not dose related. The largest mean changes occurred on Cycle 2 Day 1 and were 10 ms (UCL: 14.6 ms) and and 5 ms (UCL: 6.8 ms) for duvelisib 25 mg BID and duvelisib 75 mg BID, respectively. Furthermore, 16 (8%) subjects had a PR>220 ms.

One subject ((b) (6) 25 mg dose) had a non-serious adverse event of AV block, first degree. This subject had a baseline PR value of 194 ms. Post-treatment PR values were >200 ms with the largest increase of 31 ms from baseline (PR=225 ms).

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	25 mg BID	
Maximum tolerated dose	75 mg BID	
Principal adverse events	Dose limiting adverse events at 100 mg BID were Grade 3 rash and Grade 3 ALT/AST elevation. The most common (>10%) expected AEs (all Grades) in subjects with CLL/SLL or FL regardless of causality are diarrhea, neutropenia, pyrexia, headache, nausea, anemia, cough, pneumonia, constipation, upper respiratory tract infection, vomiting, thrombocytopenia, bronchitis, colitis, decreased appetite, fatigue, asthenia, weight decreased, abdominal pain, dyspnea, rash, back pain, edema peripheral, arthralgia, asthenia, ALT/AST increase, and hypokalemia.	
Maximum dose tested	Single Dose	30 mg (healthy subjects)
	Multiple Dose	100 mg BID (oncology subjects); maximum tolerated dose = 75 mg BID (oncology subjects)
Exposures Achieved at Maximum Tested Dose	Single Dose (30 mg in healthy subjects)	Mean (%CV) C_{max} (ng/mL) 1140 (38%); n=4 AUC_{0-inf} (ng*h/mL) 3395 (38%); n=4
	Multiple Dose (75 mg BID for 28 days in oncology subjects)	Mean (%CV)) C_{max} (ng/mL) 3294 (51%); n=90 AUC_{0-12} (ng*h/mL) 19059 (59%); n=81
Range of linear PK	Healthy subjects: 1-30 mg following single oral dose 1-5 mg BID (largest range tested) following 14 days of dosing Oncology subjects: Mean C_{max} increased 2.2-fold and AUC_{tau} increased 2.4-fold across the dose range of 25 mg BID to 75 mg BID.	
Accumulation at steady state	Mean (%CV) = 1.94-fold (50.8%) at 25 mg BID	
Metabolites	• IPI-656 (mono-oxidation): Primary metabolite which accounted for 45.8% of total radioactivity in 0-120 hour pooled human plasma. IC_{50} > 3.5 μM against PI3K-α, -β, -δ, and –γ in biochemical assays. No significant binding to 442 diverse kinases (tested at 1 μM). Little to no activity in competitive binding assays against a panel of 50 GPCRs, ion channels and transporters (tested at 10 μM). • Two minor metabolites M7 (glucuronidation) and M20 (N-oxidation) were also detected in plasma at low levels (i.e. <4% total radioactivity in 0-120 hour pooled human plasma).	
Absorption	Absolute/Relative Bioavailability	Mean (%CV) abs. bioavailability = 42% (23%)
	T_{max}	Median (range) for duvelisib = 0.89 h (0.5, 3.0)

<table>
<tr><td></td><td></td><td>Median (range) for IPI-656 = 3.5 h (2.0, 6.0)</td></tr>
<tr><td>Distribution</td><td>Vss/F</td><td>Mean (%CV) V_{ss} = 28.5 L (62%)</td></tr>
<tr><td></td><td>% bound</td><td>Mean (%CV) = 98.54% (27%) (healthy subjects)
Mean (%CV) =99.00% (44%) (oncology subjects)</td></tr>
<tr><td>Elimination</td><td>Route</td><td>Hepatobiliary: 79% of administered dose
Renal: 13.5% of administered dose</td></tr>
<tr><td></td><td>Terminal t½</td><td>Mean (%CV) for duvelisib = 4.7 h (56.9%)
Mean (%CV) for IPI-656 = 14.2 (54%)</td></tr>
<tr><td></td><td>CL/F or CL</td><td>Mean (%CV) CL = 4.2 L/h (55.5%)</td></tr>
<tr><td>Intrinsic Factors</td><td>Age
Sex
Race</td><td>Based on population PK, the effects of age, gsex, and race were not considered to have clinically significant impact on duvelisib PK.</td></tr>
<tr><td></td><td>Hepatic & Renal Impairment</td><td>Mean change in C_{max} and AUC in subjects with hepatic impairment compared with healthy control subjects following a single 25 mg dose:
<table>
<tr><td>Parameter</td><td colspan="3">Degree of impairment</td></tr>
<tr><td></td><td>Mild</td><td>Moderate</td><td>Severe</td></tr>
<tr><td>C_{max}</td><td>↑28%</td><td>↓22%</td><td>↓39%</td></tr>
<tr><td>AUC_{inf}</td><td>↓11%</td><td>↓6%</td><td>↓19%</td></tr>
<tr><td>$C_{max,u}$ [a]</td><td>↑61%</td><td>↑4%</td><td>↑14%</td></tr>
<tr><td>$AUC_{inf,u}$ [a]</td><td>↑12</td><td>↑25%</td><td>↑51%</td></tr>
</table>
a: based on unbound plasma concentrations

The effect of renal impairment will be evaluated using population PK methods.</td></tr>
<tr><td>Extrinsic Factors</td><td>Drug interactions</td><td>
<table>
<tr><td></td><td>Observed Ratio[a]</td></tr>
<tr><td colspan="2">Duvelisib exposure ratio with/without ketoconazole [b]</td></tr>
<tr><td>C_{max}</td><td>1.66 (1.48, 1.86)</td></tr>
<tr><td>AUC</td><td>3.95 (3.66, 4.25)</td></tr>
<tr><td colspan="2">Duvelisib exposure ratio with/without rifampin [c]</td></tr>
<tr><td>C_{max}</td><td>0.34 (0.30, 0.39)</td></tr>
<tr><td>AUC</td><td>0.18 (0.16, 0.21)</td></tr>
<tr><td colspan="2">Midazolam exposure ratio with/without duvelsib [d]</td></tr>
<tr><td>C_{max}</td><td>2.20 (1.87, 2.58)</td></tr>
<tr><td>AUC</td><td>4.29 (3.76, 4.88)</td></tr>
</table>
a: Geometric mean ratio (90% CI)
b: Duvelisib 10 mg single dose with/without ketoconazole 200 mg BID
c: Duvelisib 25 mg single dose with/without rifampin 600 mg QD
d: Midazolam 2 mg oral single dose with/without duvelisib 25 mg BID</td></tr>
<tr><td></td><td>Food Effects</td><td>C_{max} decreased 37%; AUC_{last} and AUC_{inf} are not affected by a high-fat meal</td></tr>
</table>

Expected High Clinical Exposure Scenario	The high clinical exposure scenario is the concomitant administration of duvelisib with a strong CYP3A inhibitor. C_{max} after a single dose of duvelisib 10 mg in combination with steady state ketoconazole was 1.7-fold higher compared to duvelisib alone. This is less than the 2.4-fold increase in C_{max} observed in oncology subjects at the maximum dose tested (75 mg BID) compared with the therapeutic dose (25 mg BID). AUC after a single dose of duvelisib 10 mg in combination with steady state ketoconazole was 4.0-fold higher compared to duvelisib alone. Duvelisib is both a substrate for and an inhibitor of CYP3A. As a result, duvelisib systemic clearance is reduced ~30-40% at steady state compared with a single dose due to auto-inhibition and decreased CYP3A activity. PBPK modeling predicts the increase in C_{max} and AUC with a strong CYP3A inhibitor when duvelisib is dosed to steady state is 1.36-fold and 1.59-fold, respectively. Steady state exposures observed at 75 mg BID (maximum tolerated dose) are higher than those predicted by the PBPK model for co-administration of 25 mg BID with a strong CYP3A inhibitor.
Preclinical Cardiac Safety	The IC_{50} values for duvelisib and metabolite IPI-656 for hERG inhibition were 49.8 μM and >100 μM, respectively, in GLP in vitro hERG studies. These high IC_{50} values, along with the high degree of plasma protein binding of the molecules (~1% free in human plasma for both compounds at clinically relevant plasma concentrations), suggest a low potential for QT prolongation in humans. The ratio of the hERG IC_{50} to steady state free C_{max} is 1395 for duvelisib and 3868 for IPI-656. Duvelisib showed no adverse effects in the cardiovascular system up to 150 mg/kg (C_{max} ~ 5.3 μM; IC_{50}: free C_{max} ratio 94 assuming free fraction of 10%) in a GLP cardiovascular study in cynomolgus monkeys.
Clinical Cardiac Safety	Duvelisib been studied in nineteen Verastem sponsored studies and 1344 subjects received at least 1 dose of duvelisib at any dose level. Six MedDRA broad Standard Medical Queries (SMQs): *Torsades de Pointes*, Sudden Death, Ventricular Tachycardia, Ventricular fibrillation-flutter, Syncope and Seizure were used to identifying subjects with potential QT-related events who received duvelisib as part of clinical development program. This wide net swept up 44 subjects, but only 4 were relevant with respect to QT issues. Review of ECG intervals from these subjects showed, however, that only 2 of 4 had QTcF prolongation (QTcF>450 msec); and both of them had prolongation before receiving any duvelisib. Clinical experience linking duvelisib with QT prolongation is minimal or non-existent. In addition to above-mentioned analyses, the results from exposure-response analyses indicated only less than 1.5% of subjects had a Fridericia's corrected QT interval (QTcF) >500 msec and change from Baseline in QTcF ≥60 msec.

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/s/

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Division of Hematology Products (DHP) Labeling Review at Filing

NDA Number	**211155**
Application Type	**NME**
Proprietary Name **(nonproprietary name)**	**Proposed: Copiktra** **(duvelisib)**
Receipt Date	**02/05/18**
PDUFA Goal Date **(Internal Goal Date)**	**TBA**
Review Classification	**TBA**
Proposed Indication (or current indication if unchanged)	**CLL, SLL, FL**
Dosing Regimen	**25 mg orally daily**
From	**Virginia Kwitkowski, MS, ACNP-BC** **Associate Director for Labeling, DHP**

Background of Application:

The NDA for duvelisib, a kinase inhibitor, was submitted on February 5, 2018.

In this filing review, I propose initial, high-level, labeling recommendations and edits in the Copiktra 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 Copiktra. These comments should be sent to the Applicant so that they can make revisions before the FDA review team begins work on the Prescribing Information.

The following pages contain the proposed labeling from the Applicant with my recommended edits in text and comments explaining the revisions in balloons. Given that the scientific review of the labeling has just begun, my labeling recommendations in this review should be considered preliminary and may not represent DHP's final recommendations for the Copiktra Prescribing Information.

35 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

VIRGINIA E KWITKOWSKI
02/08/2018