CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216059Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

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:	January 5, 2023
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 216059
Product Name and Strength:	Jaypirca (pirtobrutinib) tablets, 50 mg, 100 mg
Applicant/Sponsor Name:	Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company (Loxo)
OSE RCM #:	2021-2379-1
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on December 22, 2022 for Jaypirca. We reviewed the revised container labels for Jaypirca (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] We note the Applicant did not include the statements, (b) (4) on the principal display panel of the container labels to avoid crowding of the information.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Iverson, N. Label and Labeling Review for Jaypirca (NDA 216059). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 OCT 20. RCM No.: 2021-2379.

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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:	December 28, 2022
To:	Denise Felluca, PharmD, MBA Regulatory Project Manager **Division of Hematologic Malignancies II (DHM2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Laurie Buonaccorsi, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Jennifer Chen, PharmD, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	JAYPIRCA (pirtobrutinib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 216059
Applicant:	Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company

1 INTRODUCTION

On May 27, 2022, Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company, submitted for the Agency's review an original New Drug Application (NDA) 216059 for JAYPIRCA (pirtobrutinib) tablets. The proposed indication is for the treatment of adult patients with mantle cell lymphoma (MCL) who have previously been treated with a Bruton Tyrosine Kinase (BTK) inhibitor.

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 Hematologic Malignancies II (DHM2) on June 7, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for JAYPIRCA (pirtobrutinib) tablets.

2 MATERIAL REVIEWED

- Draft JAYPIRCA (pirtobrutinib) tablets PPI received on May 27, 2022, and received by DMPP and OPDP on December 13, 2022.
- Draft JAYPIRCA (pirtobrutinib) tablets Prescribing Information (PI) received on May 27, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 13, 2022.
- Approved IMBRUVICA (ibrutinib), CALQUENCE (acalabrutinib), and BRUKINSA (zanubrutinib) comparator labeling dated August 24, 2022, August 3, 2022, and September 14, 2021, respectively.

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. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI 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 PPI 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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SHARON R MILLS
12/28/2022 02:29:09 PM

BARBARA A FULLER
12/28/2022 02:33:06 PM

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

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

Memorandum

Date: 12/22/22

To: Denise Felluca, PharmD, MBA, Regulatory Health Project Manager, Division of Hematologic Malignancies II (DHM2)

From: Jennifer Chen, PharmD, MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for JAYPIRCA™ (pirtobrutinib) tablets, for oral use

NDA: 216059

Background:
In response to DHM2's consult request dated June 7, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and Patient Package Insert (PPI) for the original NDA submission for JAYPIRCA™ (pirtobrutinib) tablets, for oral use.

PI/PPI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on December 13, 2022, and our comments are provided below.

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

Thank you for your consult. If you have any questions, please contact Jennifer Chen at (301) 796-9398 or Jennifer.Chen@fda.hhs.gov.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	October 20, 2022
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 216059
Product Name, Dosage Form, and Strength:	Jaypirca (pirtobrutinib) tablets, 50 mg, 100 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company (Loxo)
FDA Received Date:	May 27, 2022 and July 29, 2022
OSE RCM #:	2021-2379
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the approval process for Jaypirca (pirtobrutinib) tablets, we reviewed the proposed Jaypirca container labels, Prescribing Information (PI), and Patient Information, for areas of vulnerability that may lead to medication errors.

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 Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
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 or ISMP Newsletters 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

Loxo submitted a 505 (b)(1) application to obtain marketing approval of Jaypirca (pirtobrutinib) tablets. Jaypirca is proposed for the treatment of adult patients with Mantle cell lymphoma (MCL) who have been previously treated with a Bruton's tyrosine kinase (BTK) inhibitor.

We performed a risk assessment of the proposed container labels, PI, and Patient Information for Jaypirca tablets to determine whether there are significant concerns in terms of safety related to preventable medication errors. We identified areas of the proposed labels and labeling that could be revised to improve clarity and readability of important information. For the Division, we note lack of clarity in the administration and storage instructions. Additionally, we note abbreviations and symbols in the recommended dosage. For the Applicant, we note that the Rx only statement appears bolded and the expiration date format is undefined. We also note lack of clarity in the administration instructions. These factors may confuse the user

and inadvertently lead to medication errors. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We have identified areas in the proposed container labels, PI, and Patient Information that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for Loxo to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 2 (DHM 2)

A. Highlights of Prescribing Information

1. We recommend including the statement, “Do not cut, crush, or chew tablets.” to bring prominence to this important information and be consistent with Section 2 Dosage and Administration of the Prescribing Information.

B. Prescribing Information

1. Dosage and Administration Section
   a. As currently presented, the dosage regimen contains the abbreviation, “QD”. Error prone abbreviations may lead to misinterpretation and medication error. We recommend replacing the abbreviation, “QD” with the intended meaning, “once daily”.
   b. We recommend revising the statement, (b) (4) To “Do not cut, crush or chew tablets” (b) (4) .
   c. In Table 1: (b) (4)
2. Storage and Handling
   a. We recommend revising the storage information to appear as, “Store tablets at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F).” to be consistent with the container labels.

C. Patient Information

1. How should I use JAYPIRCA?

a. We recommend revising the statement, [redacted] (b) (4) to "Do not cut, crush or chew the tablets." to be consistent with the Prescribing Information.

2. How should I store JAYPIRCA?
   a. We recommend revising the statement, [redacted] (b) (4) to "Store JAYPIRCA at room temperature between 68° to 77°F (20° to 25°C)." to be consistent with the container labels.

4.2 RECOMMENDATIONS FOR LOXO ONCOLOGY, INC., A WHOLLY OWNED SUBSIDIARY OF ELI LILLY AND COMPANY (LOXO)

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

A. Container Labels

1. We recommend including the statements, "Swallow tablets whole. Do not cut, crush or chew the tablets." on the principal display panel to mitigate product administration errors.
2. The Rx Only statement appears prominent on the principal display panel. We recommend decreasing the prominence by debolding the Rx Only statement.
3. As currently presented, the format for the expiration date is not defined. We are unable to assess the proposed expiration date format from a medication safety perspective. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Jaypirca received on May 29, 2022 from Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company (Loxo).

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Jaypirca</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>pirtobrutinib</td></tr>
<tr><td>Indication</td><td>For the treatment of adult patients with Mantle cell lymphoma (MCL) who have been previously treated with a Bruton’s tyrosine kinase (BTK) inhibitor.</td></tr>
<tr><td>Route of Administration</td><td>Oral</td></tr>
<tr><td>Dosage Form</td><td>tablets</td></tr>
<tr><td>Strength</td><td>50 mg, 100 mg</td></tr>
<tr><td>Dose and Frequency</td><td>200 mg orally once daily
Dosage modifications to 50 mg once daily or 100 mg once daily for adverse reactions</td></tr>
<tr><td>How Supplied</td><td>
<table>
<tr><th>Tablet Strength</th><th>Description</th><th>Package Configuration</th><th>NDC Number</th></tr>
<tr><td>50 mg</td><td>Blue, film coated, arc-triangle shaped tablets debossed with “Lilly 50” on one side and “6902” on the other side.</td><td>Bottle with child-resistant closure.
Each bottle contains 30 tablets.</td><td>#####-###-##</td></tr>
<tr><td>100 mg</td><td>Blue, film coated, round tablets debossed with “Lilly 100” on one side and “7026” on the other side.</td><td>Bottle with child-resistant closure.
Each bottle contains (b) (4) 60 tablets.</td><td>(b) (4)
#####-###-##
(b) (4)</td></tr>
</table>
</td></tr>
<tr><td>Storage</td><td>Store tablets at (b) (4)</td></tr>
</table>

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 Jaypirca labels and labeling submitted by Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company (Loxo).

- Container labels received on May 27, 2022
- Prescribing Information (Image not shown) received on July 29, 2022, available from \\CDSESUB1\EVSPROD\nda216059\0023\m1\us\pirtobrutinib-uspi-final.pdf
- Patient Information received on May 27, 2022, available from \\CDSESUB1\EVSPROD\nda216059\0008\m1\us\pirtobrutinib-patient-info.pdf

G.2 Label and Labeling Images

Container labels

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

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CLINICAL INSPECTION SUMMARY

Date	October 21, 2022
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., Ph.D., Acting Branch Chief/ Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Deepti Telaraja, M.D., Medical Officer Yvette Kasamon, M.D., Ph.D., Medical Team Leader Nicole Gormley, M.D., Division Director Denise Felluca, Pharm.D., Regulatory Health Project Manager Division of Hematology Malignancies 2 (DHM2) Office of Oncology Drugs
NDA	NDA 216059
Applicant	Loxo Oncology Inc., a wholly owned subsidiary of Eli Lilly and Company.
Drug	Jaypirca™ (pirtobrutinib)
NME	Yes
Division Classification	Bruton's tyrosine kinase inhibitor
Proposed Indication	Treatment of adult patients with mantle cell lymphoma who have been treated with a Bruton's tyrosine kinase inhibitor.
Review Type	Priority Review
Consultation Request Date	July 6, 2022
Summary Goal Date	November 15, 2022
Action Goal Date	January 10, 2023
PDUFA Date	January 27, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study LOXO-BTK-18001 were submitted to the Agency in support of a New Drug Application (NDA) for the drug pirtobrutinib, proposed as treatment of adult patients with mantle cell lymphoma who have been treated with a Bruton's tyrosine kinase inhibitor. The sponsor, Loxo Oncology Inc., a wholly owned subsidiary of Eli Lilly and Company, and two clinical investigators (Luhua [Michael] Wang, M.D., and Anthony R. Mato, M.D.) were inspected for Study LOXO-BTK-18001.

Based on the overall inspection results of the sponsor and two clinical investigators, the study data derived from the clinical investigator sites, and submitted by Loxo Oncology Inc. are considered reliable.

The study data submitted to the Agency for assessment appeared acceptable in support of the proposed indication.

II. BACKGROUND

Bruton's tyrosine kinase (BTK) is a member of the "Tec" family of nonreceptor protein tyrosine kinases (which includes BTK, IL-2 inducible T-cell kinase, resting lymphocyte kinase, and bone marrow-expressed kinase and a key component of the B cell antigen receptor signaling complex. In B-cells, Bruton's tyrosine kinase signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. BTK expression is restricted to a subset of B-cells and myeloid cells, and in malignancies thought to derive from them, including mantel cell lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

Bruton's tyrosine kinase is a signaling molecule of the B-cell antigen receptor and cytokine receptor pathways. Pirtobrutinib [LOXO-305; LY3527727] is a small molecule reversible inhibitor of Bruton's tyrosine kinase.

Pirtobrutinib is proposed for treatment of adult patients with mantle cell lymphoma who have previously been treated with a Bruton's tyrosine kinase inhibitor.

Study LOXO-BTK-18001 was submitted in support of the current applicant's NDA.

Study LOXO-BTK-18001

Study LOXO-BTK-18001 was a Phase I/II, open-label, multicenter study of oral pirtobrutinib to evaluate safety and efficacy in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and Non-Hodgkin's Lymphoma (NHL) who have failed or were intolerant to standard of care. This clinical investigative study comprised two portions: monotherapy and combination therapy. The monotherapy portion consisted of a Phase 1 dose escalation and dose expansion, as well as Phase 2 study. The combination therapy Phase 1b portion was a safety assessment and expansion of pirtobrutinib in combination with venetoclax with or without anti-CD20 therapy (rituximab).

Pirtobrutinib was administered to patients in oral tablet form at dose levels depending upon dose assignment in Phase 1 (refer to Pirtobrutinib Dose Levels) and was administered as monotherapy in Phase 2 and as part of safety assessment in combination therapy in Phase 1b. Dosing was fixed as total milligram as opposed to weight or body surface area-based). The starting dose of pirtobrutinib was 25 mg once daily.

In Phase 1b of the study, patients with relapsed CLL/SLL were enrolled to one of two combination treatment arms (pirtobrutinib plus venetoclax [Arm A] or pirtobrutinib plus venetoclax plus rituximab [Arm B]).

Phase 2 included seven disease defined cohorts as follows:

- Cohort 1: Non-blastoid mantle cell lymphoma patients treated with a prior Bruton's tyrosine kinase (BTK) (inhibitor-containing regimen

- Cohort 2: CLL/SLL patients treated with 2 or more prior regimens, including a BTK inhibitor-containing regimen

- Cohort 3: CLL/SLL patients with no prior therapy
- Cohort 4: CLL/SLL patients treated with prior therapy, BTK inhibitor naïve
- Cohort 5: Waldenström macroglobulinemia patients treated with a prior BTK inhibitor-containing regimen
- Cohort 6: Marginal zone lymphoma patients treated with a prior BTK inhibitor-containing regimen
- Cohort 7: Defined as CLL/SLL or NHL not otherwise specified in Cohorts 1 through 6, inclusive of CLL/SLL, Richter's transformation, or low-grade NHL with transformation, blastoid mantle cell lymphoma, and/or patients with history of central nervous system involvement or primary CNS lymphoma. In the event the Sponsor electively closed Cohorts 2 through 4 prior to completion, patients with CLL/SLL who were ineligible to participate in or unable to access late phase studies of pirtobrutinib may be eligible to enroll in this cohort. Patients enrolling to Cohort 7 must have received one or more prior therapies, or no available approved therapy with demonstrated clinical benefit.

Subjects with diffuse large B cell lymphoma or mantle cell lymphoma without prior Bruton's tyrosine kinase inhibitor treatment were excluded from the study.

The primary objective of the monotherapy Phase 1 portion of the study was to determine the maximum tolerated dose)/recommended Phase 2 dose of oral pirtobrutinib in patients with previously treated CLL/SLL and B-cell NHL.

The primary objective of the monotherapy Phase 2 portion of the study was to assess the preliminary antitumor activity of pirtobrutinib based on overall response rate as assessed by an Independent Review Committee.

The primary safety endpoint, principally for the Phase 1 study involved an assessment of patient and drug safety. For example, safety included the incidence and nature of drug limiting toxicities in dose escalation phase, the incidence, nature, and severity of adverse events.

The primary efficacy endpoint for this Phase 2 study was objective response to treatment by appropriate disease-defined criteria and assessed by Independent Review Committee.

For the proposed indication, the verification of the efficacy endpoints was requested for Phase 2 Cohort 1 subjects with mantle cell lymphoma only for clinical inspection purposes. All subjects in the study were part of safety evaluation.

Study LOXO-BTK-18001 had enrolled 725 patients (including 164 patients with mantle cell lymphoma) in 49 study sites. The first study patient enrolled was treated on 21 March 2019. The data cut-off (for analyses and interim reporting) was 31 January 2022. This study is ongoing.

III. RESULTS in Study LOXO-BTK-18001

1. Luhua (Michael) Wang, M.D./Site 111

M.D. Anderson Cancer Center
1515 Holcombe Boulevard Unit 24
Houston, TX 77030-4000

Inspection dates: August 23 - 26, 2022

At Site 111, a total of 63 study subjects for all seven study cohorts were screened, and 54 study subjects were enrolled. Of those enrolled, 43 study subjects completed the study. There were 11 study subjects who discontinued due to unspecified reasons. For Phase 2 Cohort 1 (mantle cell lymphoma cohort), which is the interest of this site audit, 11 study subjects were enrolled.

A 100% of the study subject records' informed consent documents were evaluated. All the enrolled study subject medical records were in paper format. The following documents were examined: study site training records, clinical patient history and physical examination; adverse event reporting, efficacy, concomitant medication records, protocol adherence, investigational product dosage, drug accountability. Source and regulatory documents were available in both paper and electronic format. Source records were reviewed for the 54 enrolled subjects in this clinical investigation.

The primary efficacy endpoint data in the source documents, with the raw data line listings provided, were verified during the study site inspections for the Phase 2 Cohort 1 study enrolled subjects. Records were also assessed for adverse events and serious adverse events. No discrepancies were noted.

A Form FDA 483, Inspectional Observations, was not issued at the end of the site inspection.

2. Anthony R. Mato, M.D./Site 104

Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, NY 10065-6007

Inspection dates: September 12 - 16, 2022

At Site 104, a total of 103 subjects were screened, and 90 subjects were enrolled to participate. Of the 90 subjects enrolled, a total of 12 subjects discontinued from the study: four subjects withdrew from the study, and eight subjects discontinued due to adverse events.

For Phase 2 Cohort 1, the inspection focused on the mantle cell lymphoma cohort which involved 12 subjects. None of the subjects from this cohort remained on treatment.

Institutional Review Board-informed consent forms for all subjects in Phase 2 Cohort 1 were assessed. All enrolled 12 study subject records were reviewed for eligibility, general protocol adherence, required procedures and evaluations including data collection methods, drug storage, administration of the investigational study product adverse and serious events, primary study efficacy endpoints. Source records were compared to the provided data line listings for inspections.

Source records for all the Phase 2 Cohort 1 enrolled study patients were examined and verifiable for primary endpoint data against the data line listings. No discrepancies were noted. There was no evidence of under-reporting of adverse events and serious adverse events.

No Form FDA 483, Inspectional Observations, was issued at the end of the inspection.

3. Loxo Oncology, Inc./(Sponsor)
201 Haskins Way, Suite 220
South San Francisco, California 94080

Inspection dates: September 2 - 9, 2022

Loxo Oncology, Inc. is a wholly owned subsidiary of Eli Lilly and Company and the sponsor of this application.

The site audit of the sponsor focused the inspection on selection and monitoring of clinical investigators, selection of monitors, monitoring procedures and activities, quality assurance, safety/adverse event reporting, data collection and handling, records retention, financial disclosure, and electronic records. Monitoring documents for U.S. Sites 104, 111, 107, and 113, plus ex-U.S. Site 301, were evaluated.

At the end of the sponsor site audit, no FDA Form 483 (List of Inspectional Observations) was issued. The following items were discussed at the site close-out inspection meeting: (a) Training for 24-hour rotating physicians after-hours care (mainly clinical sub-investigators) was optional, (b) For the adverse events queries report, the audit found eight open queries that were not closed within the query resolution turn-around time, as outlined in of the study monitoring plan, (c) Informed consent form source data were not verified at all remote monitoring visits, (d) Not all monitors selected were qualified based on training/experience and monitor job descriptions, and (d) A percentage of 100% source data verification may be conducted as part of standard source data verification practice. For performing reduced source data verification, however, the applicant did not define (nor specify) the high enrolling sites that were part of a reduced source data verification plan, according to the submitted study monitoring procedures.

Reviewer's comments:
A comprehensive evaluation of the monitoring reports was performed during the inspection. All the adverse events and serious adverse events were reported to the FDA. The aforementioned items discussed at the clinical study site close-out meeting were not considered significant.

In general, the sponsor oversight and monitoring of study sites appeared to be acceptable. No objectionable FDA findings were observed.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Office of Scientific Investigations

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JENN W SELLERS
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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA-216059
Submission Number	008
Submission Date	05/27/2022
Date Consult Received	06/07/2022
Drug Name	Pirtobrutinib
Indication	Mantle Cell Lymphoma
Therapeutic Dose	200 mg, Once daily
Clinical Division	DHM2
Protocol Review	Link

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

This review responds to your consult dated 6/7/2022 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT reviews for IND-139876 dated 01/29/21 in DARRTS (link);
- Previous IRT reviews for IND-139876 dated 11/17/20 in DARRTS (link);
- Sponsor's clinical study protocol # LOXO-BTK-20011 (SN0008; link);
- Sponsor's clinical study report # LOXO-BTK-20011 (SN0008; link);
- Sponsor's statistical analysis plan # LOXO-BTK-20011 (SN0008; link);
- Sponsor's cardiac safety report # LOXO-BTK-20011 (SN0008; link);
- Sponsor's proposed product label (SN0008; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0008; link).

1 SUMMARY

No significant QTcF prolongation effect of pirtobrutinib was detected in this thorough QT (TQT) study assessment.

The effect of pirtobrutinib was evaluated in a TQT study (Study # LOXO-BTK-20011). This was a double-blind (open-label moxifloxacin), randomized, single-dose (900 mg), placebo- and positive-controlled, (3-way) crossover study. Assay sensitivity was established using oral moxifloxacin (400 mg single dose). The highest dose evaluated was 900 mg (as a single dose), which offers ~2-fold margin over the therapeutic exposures (Cmax: 6460 ng/mL) associated with the maximum proposed dose at the steady state and expected to cover the current high clinical exposure scenario (Section 3.1). However, the hepatic impairment study is still pending.

Data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that pirtobrutinib is associated with significant QTc prolonging effect (refer to Section 4.5) – see Table 1: Point Estimates and the 90% CIs (FDA Analysis) for overall

results. Findings of this analysis are further supported by the available by-time analysis (Section 4.3) and absence of ECG outliers in categorical analysis (Section 4.4).

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

ECG parameter	Treatment	Concentration (ng/mL)	ΔΔQTcF (msec)	90% CI (msec)
QTc	Pirtobrutinib 900 mg	14,280	0.7	(-1.2 to 2.6)

For further details of the FDA analysis, please see Section 4.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

With pending hepatic impairment study (Study # LOXO-BTK-20012), it is unclear if the TQT study covers the steady state exposures of pirtobrutinib (Cmax,ss) in patients with severe hepatic impairment at the approved recommended dose (i.e., without dose reduction).

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN008 (link) from the CSS-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 a single 900 mg dose of pirtobrutinib (equivalent to approximately 2 times higher than the concentrations achieved at steady state at the recommended dosage of 200 mg once daily) on the QTc interval was evaluated in a placebo-controlled and positive-controlled study in 30 healthy subjects. Pirtobrutinib had no clinically meaningful effect on the change in QTcF interval (i.e., > 10 ms) and there was no relationship between pirtobrutinib exposure and change in QTc interval.*~~

At a dose 2 times the maximum approved recommended dose, <TRADENAME> does not prolong the QT interval to any clinically relevant extent.

We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Loxo Oncology, Inc. is developing pirtobrutinib for the treatment of patients with mantle cell lymphoma (who have previously been treated with a Bruton's tyrosine kinase inhibitor). Pirtobrutinib (LOXO-305; MW: 479.44, (b) (4) is an inhibitor of the human Bruton's tyrosine kinase (BTK, ATP-competitive, reversible, noncovalent inhibitor). The sponsor states that the B-cell malignancies are known to be dependent on BTK activity for growth and survival. Refer to the previous IRT review for IND-139876 dated 11/17/2020 and 01/28/2021 in DARRTS.

The product is formulated as immediate-release, film-coated tablet formulation containing 50 or 100 mg pirtobrutinib for oral administration. The maximum proposed therapeutic dose for the present indication is 200 mg once daily (with or without food). The peak concentrations of 6460 ng/mL (Tmax: ~2 h; half-life: ~22 h) are expected at steady-state with the anticipated therapeutic dose (Cycle 1 Day 8; Study # LOXO-BTK-18001). The sponsor expects moderate accumulation at steady state with the proposed maximum therapeutic dose (Cmax Racc: ~2-fold).

The studies indicate that pirtobrutinib undergoes oxidative, hydrolytic, and direct glucuronidation with parent constituting the majority (73%) of the drug-related exposure in human plasma. Sponsor claims that pirtobrutinib metabolized by multiple enzymes (by CYP3A4, UGT1A8, and UGT1A9) and highlights that it has a low drug interaction potential as a victim drug. Concomitant administration of pirtobrutinib with a strong inhibitor of CYP3A4 (e.g., itraconazole) is expected to result in increased exposures of pirtobrutinib (AUC: ~1.5-fold) without considerable changes in the peak concentrations (Cmax: 1.04-fold; Study # LOXO-BTK-20006). The human mass balance study indicates that 37% of the drug (as TR; 18% unchanged) is excreted in feces, and 57% of the drug (as TR; 10% unchanged) is excreted in urine (Study # LOXO-BTK-20007). Moderate increase in exposure (AUC: 1.4-fold) of pirtobrutinib was observed in subjects with severe renal impairment (Study # LOXO-BTK-20013). The sponsor proposed (b) (4) . Clinical pharmacology study characterizing potential worst-case scenario for the parent drug due to organ impairment (hepatic impairment, Study # LOXO-BTK-20012) is pending. The sponsor expects no significant increase in exposure of pirtobrutinib in patients with mild hepatic impairment proposed no dose adjustment in these population. The effect of moderate or severe hepatic impairment is unknown and the proposed label describes that the safety of pirtobrutinib has not been evaluated in patients with severe hepatic impairment.

Previously, the sponsor proposed to characterize the risk of QT prolongation of pirtobrutinib in a thorough QT study. The IRT reviewed this study protocol. Refer to the previous IRT review for IND-139876 dated 11/17/2020 in DARRTS. Overall, the proposed study design and analysis plan appeared acceptable to the IRT. It was recommended to include supratherapeutic dose in the study covering exposure of pirtobrutinib with intrinsic and extrinsic factors. In response to the IRT's comments, the sponsor included 900 mg as a supratherapeutic dose (b) (4) In addition, the IRT provided

other comments on QT correction method. Refer to the previous IRT review for IND-139876 dated 01/28/2021 in DARRTS. The study was completed as double-blind (open-label moxifloxacin), randomized, single-dose (900 mg), placebo- and positive-controlled, (3-way) crossover study in healthy subjects (n=30/31). The peak concentration (Cmax: ~13600 ng/mL) observed with highest dose studied (i.e., 900 mg single dose; under fasting conditions; as 36 × 25 mg tablets, over-encapsulated) is expected to offer only ~2.1-fold margin over the therapeutic exposures (Cmax: 6460 ng/mL) associated with the maximum proposed dose at the steady state. With pending hepatic impairment study, it is unclear if the TQT study covers the steady state exposures of pirtobrutinib (Cmax,ss) in patients with severe hepatic impairment at the proposed doses.

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the sponsor's highlights of clinical pharmacology and clinical safety.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for pirtobrutinib was based on exposure-response analysis, please see Section 3.2.3 for additional details. The largest upper bound 90% confidence interval of ΔΔQTcF in Pirtobrutinib 900 mg treatment group is less than 10 msec.

Reviewer's comment: *The sponsor provided the profiles of ΔQTcF, ΔΔQTcF, ΔHR, ΔΔHR, ΔPR, ΔΔPR, ΔQRS, and ΔΔQRS for pirtobrutinib. The profiles for mean values by time are similar to reviewer's analysis results. Please see Section 4.3 for more details.*

3.2.1.1 Assay Sensitivity

The study included oral moxifloxacin 400 mg as a positive control to detect small increases from baseline for QTcF. The sponsor's analysis indicates that relationship between moxifloxacin concentration and ΔΔQTcF was statistically significant (0.0061 msec per ng/mL [90% CI: 0.00509 to 0.00716; p-value < 0.0001]) and the lower bound of the predicted ΔΔQTcF effect using this model was above 5 msec (12.07 msec [90% CI: 10.74 to 13.41]) at the observed geometric mean peak plasma level of moxifloxacin (1786.5 ng/mL).

Reviewer's comment: *The assay sensitivity results of the reviewer's analysis agreed with the sponsor's conclusion that the study demonstrated assay sensitivity. Please see Sections 4.5.1 & 4.3.1.1 for additional details.*

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or >60 msec over baseline), HR (<50 beats/min and 25% over baseline or >100 beats/min and 25% over baseline), PR (>200 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *The sponsor's results are similar to the reviewer's results. However, in our analysis, we grouped minimum HR by ≤45 beats/min or >45 beats/min and maximum HR by ≤100 beats/min or >100 beats/min, PR by >220 msec or ≤220 msec and QRS by >120 msec or ≤120 msec. Please see Section 4.4 for more details.*

3.2.3 Exposure-Response Analysis

As a primary analysis, the sponsor performed PK/PD analysis to explore the relationship between concentration of pirtobrutinib and ΔΔQTcF (placebo corrected change from baseline in QTcF) using a linear mixed-effects approach.

The sponsor analysis indicates a concentration dependent increase in QTcF with a slight positive slope of 0.00017 msec/ng/mL (90% CI 0.000013 to 0.000336 msec/ng/mL; P value: 0.0764). The model predicted ΔΔQTcF (upper confidence interval) values of 0.73 (2.64) msec at the mean peak concentrations for the highest dose studied (900 mg single dose: geomean Cmax ~14279.6 ng/mL) following single oral administration. The results of the sponsor's analysis suggest an absence of significant QTc prolongation at the proposed therapeutic dose (i.e., 200 mg once daily).

Reviewer's comment: *The results of the reviewer's analysis agreed with the sponsor's conclusion. Please see Section 4.5 for additional details.*

3.2.4 Safety Analysis

There were no deaths or serious adverse events (SAEs) in Study LOXO-BTK-20011. All events were mild in severity. One subject discontinued the treatment after experiencing TEAEs of ALT increased and AST increased following a single dose of placebo.

Following the administration of 900 mg pirtobrutinib, no individual subject had a QTcF value 450 msec or an increase from baseline in QTcF > 30 msec.

Reviewer's comment: *No events identified to be of clinical importance per the ICH E14 guidelines (i.e., unexplained syncope, seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall, ECG acquisition and interpretation in this study appear acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associations among repeated measures within the period.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. The maximum ΔΔQTcF values by treatment are shown in Table 2.

Figure 1: Mean and 90% CI of ΔΔQTcF Time-course (unadjusted CIs).

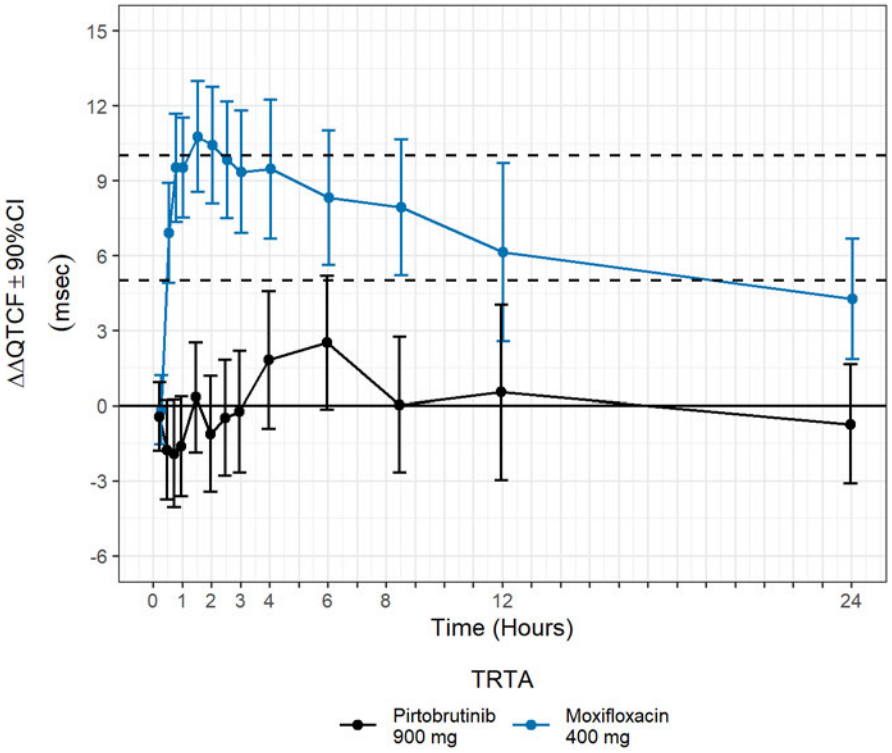


Table 2: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF

Actual Treatment	Nact / Npbo	Time (Hours)	ΔΔQTCF (msec)	90.0% CI (msec)
Pirtobrutinib 900 mg	30 / 30	6.0	2.5	(-0.2 to 5.2)

4.3.1.1 Assay Sensitivity

The primary method for establishing assay sensitivity for this study was based on exposure-response analysis - see Section 4.5.1.1 for details. Assay sensitivity is also demonstrated in the by-time analysis.

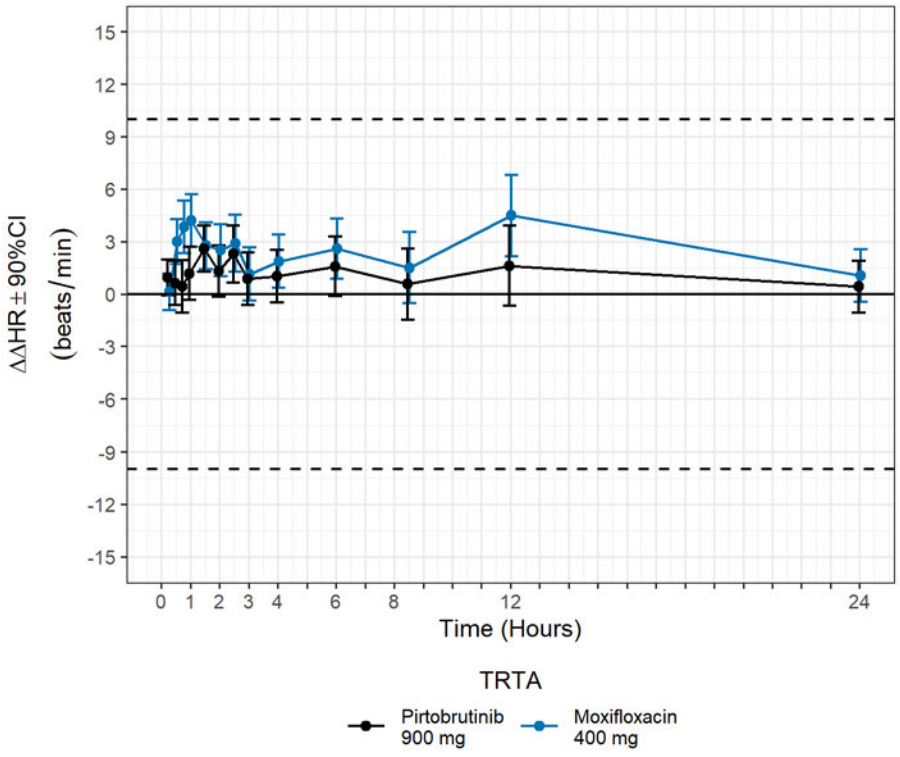
Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTcF

Actual Treatment	Nact / Npbo	Time (Hours)	ΔΔQTCF (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	29 / 30	1.5	10.8	(8.5 to 13.0)	(7.7 to 13.8)

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

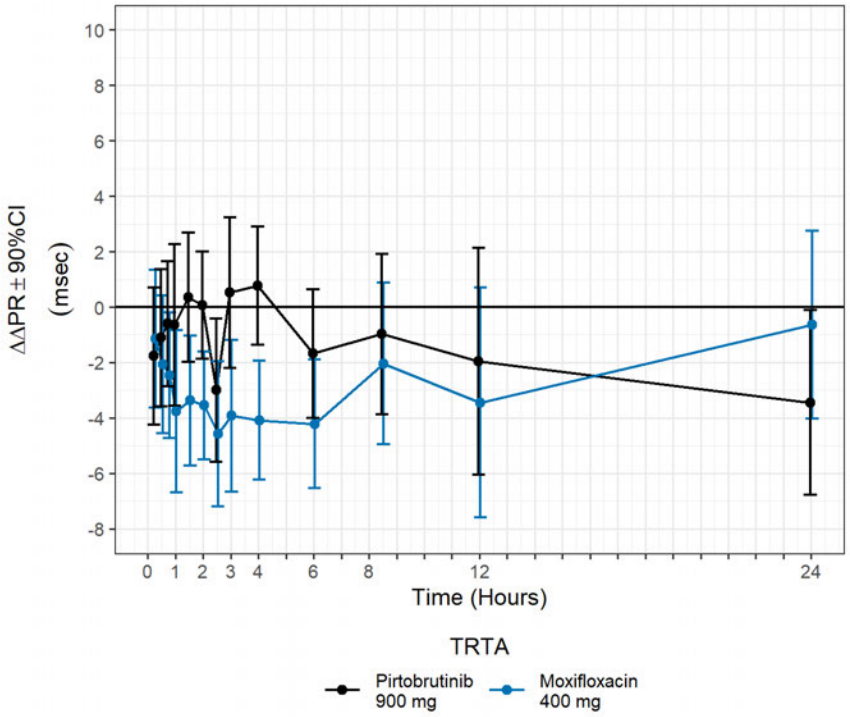
Figure 2: Mean and 90% CI of ΔΔHR Time-course



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

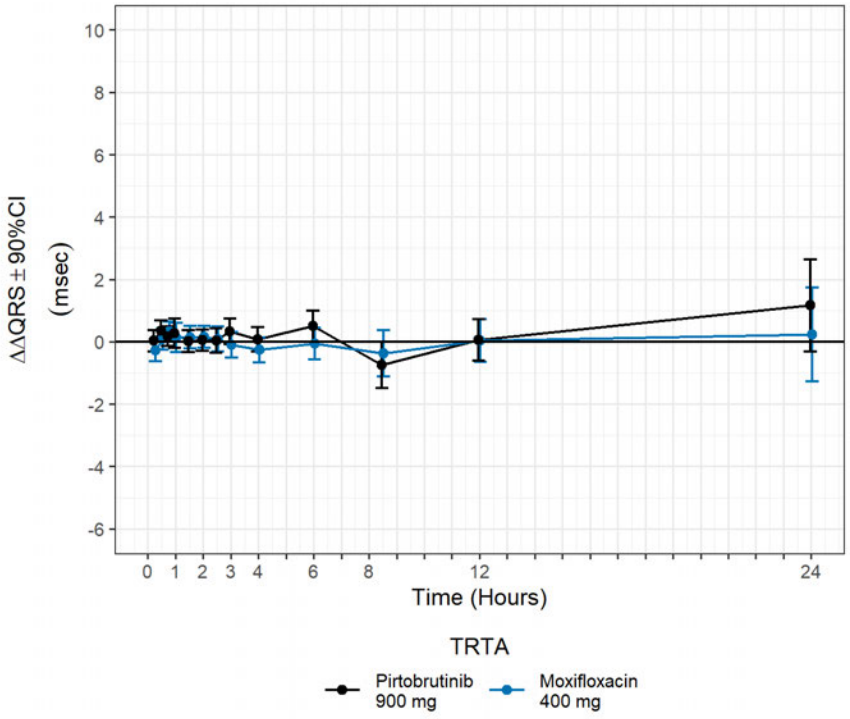
Figure 3: Mean and 90% CI of ΔΔPR Time-course



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

There were no subjects who experienced QTcF >480 msec. There were no subjects who experienced ΔQTcF >60 msec.

4.4.2 HR

There were no subjects who experienced HR >100 beats/min.

4.4.3 PR

There were no subjects who experienced PR values >220 msec.

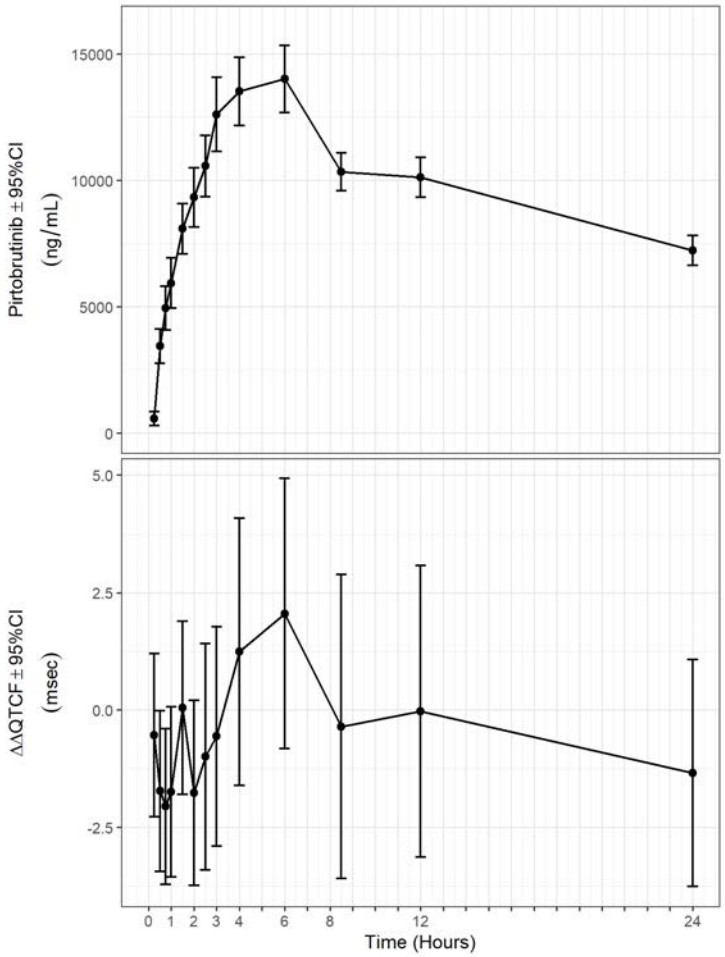
4.4.4 QRS

There were no subjects who experienced QRS values >120 msec.

4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of this analysis was to assess the relationship between plasma concentration of pirtobrutinib and ΔΔQTcF. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK. Prior to evaluating the relationship between pirtobrutinib concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: absence of - 1) significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between pirtobrutinib concentration and ΔΔQTc and 3) a non-linear relationship.

Figure 5: Time-course of Pirtobrutinib Concentration (top) and QTcF (bottom)[1]

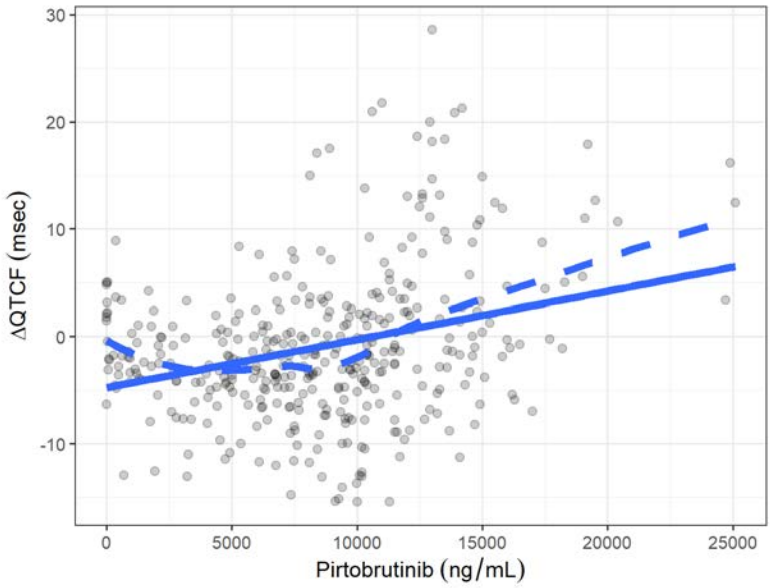


An evaluation of the time-course of pirtobrutinib concentration and changes in ΔΔQTcF is shown in Figure 5. There was no apparent delay between the time at maximum effect on ΔΔQTcF and peak concentrations of pirtobrutinib indicating no significant hysteresis.

[1] ΔΔQTcF shown were obtained via descriptive statistics and might differ from **Figure 1**

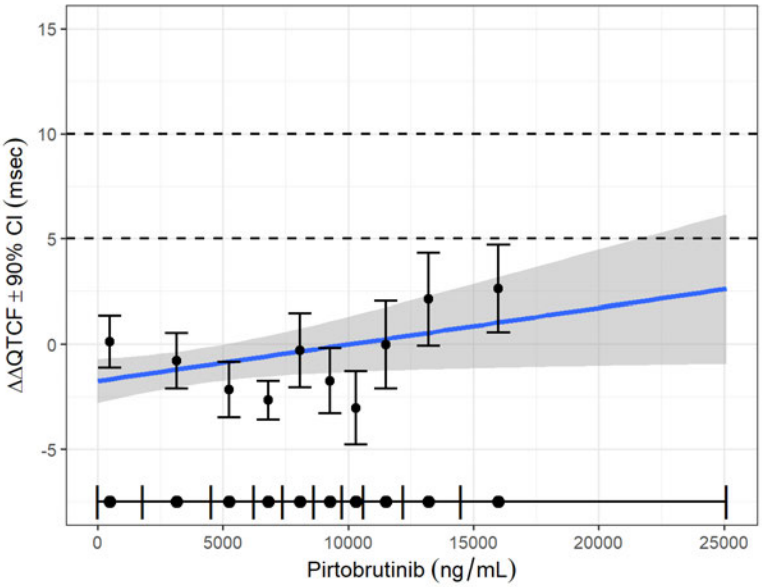
Figure 2 shows the time-course of ΔΔHR, which shows an absence of significant ΔΔHR changes and the maximum change in heart rate is below 8 bpm (Sections 4.3.2 and 4.4.2).

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between pirtobrutinib concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. **Figure 6** shows the relationship between pirtobrutinib concentration and ΔQTcF and supports the use of a linear model. Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in **Figure 7**. Predictions from the concentration-QTcF model are provided in **Table 1**.

Figure 7: Goodness-of-fit Plot for QTcF



4.5.1.1 Assay Sensitivity

To demonstrate assay sensitivity, the sponsor included oral moxifloxacin 400 mg as a positive control detecting small increases from baseline for QTcF in this study. The PK profile in the moxifloxacin group is generally consistent with the ascending, peak, and descending phases of historical data (*data not shown*). Concentration-response analysis of moxifloxacin data indicated a positive slope in the relationship between ΔΔQTcF and the plasma concentration of moxifloxacin. The lower limit of the two-sided 90% confidence interval at the observed mean peak concentrations of moxifloxacin is above 5 msec. Therefore, assay sensitivity is established.

Figure 8: Goodness-of-fit plot of ΔΔQTcF for Moxifloxacin

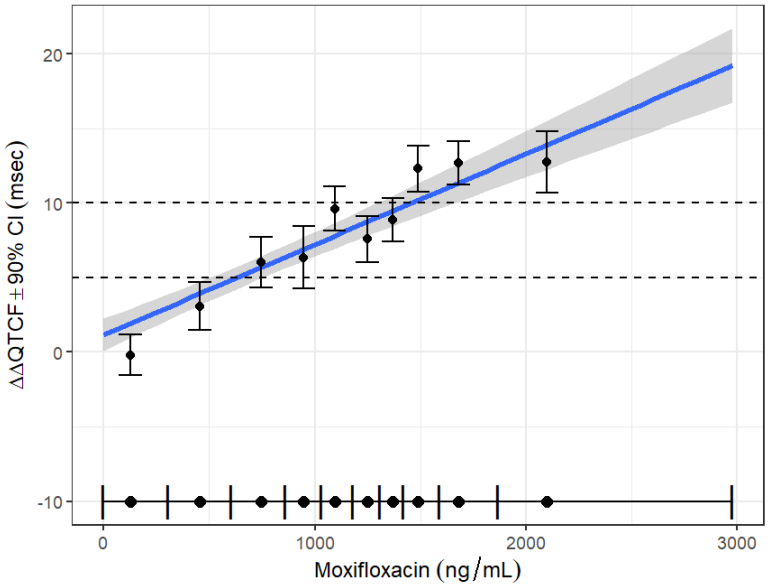


Table 4: Predictions from Concentration-QTcF Model for Moxifloxacin

Treatment	Analysis Nominal Period Day (C)	Moxifloxacin (ng/mL)	ΔΔQTcF (msec)	90.0% CI (msec)
Moxifloxacin 400mg	1	1,779.9	12	(10.6 to 13.3)

The goodness-of-fit plot for moxifloxacin is shown in **Figure 8** and the predicted QTc at the geometric mean Cmax is listed in **Table 4**. Assay sensitivity was also established using by time analysis. Please see Section 4.3.1.1 for additional details.

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/s/

DEVI KOZELI on behalf of YU-TING WENG
08/30/2022 02:03:48 PM
Signing on behalf of Yu-Ting as he is OOO

DALONG HUANG
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GIRISH K BENDE
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