CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213973Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: April 28, 2020

To: Leah Her, MS, PMP, Regulatory Project Manager, Division of Oncology 3 (DO3)

Stacy Shord, Associate Director for Labeling

From: Robert Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for QINLOCK (ripretinib) tablets, for oral use

NDA: 213973

In response to DO3's consult request dated December 16, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for Qinlock.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DO3 (Leah Her) on April 17, 2020, and are provided below.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on April 24, 2020.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on November 19, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

27 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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

/s/

ROBERT L NGUYEN
04/28/2020 05:13:24 PM

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:	April 24, 2020
To:	Leah Her, PharmD Regulatory Project Manager (RPM) **Division of Oncology 3 (DO3)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Robert Nguyen, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	QINLOCK (ripretinib)
Dosage Form and Route:	Tablets, for oral use
Application Type/Number:	NDA 213973
Applicant:	Deciphera Pharmaceuticals LLC

1 INTRODUCTION

On December 13, 2019, Deciphera Pharmaceuticals LLC, submitted for the Agency's review an original New Drug Application (NDA-213973) for QINLOCK (ripretinib) tablets, for oral use, for the proposed indication of use for the treatment of patients with advanced gastrointestinal stromal tumors (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib.

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 Oncology 3 (DO3) on December 16, 2019 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for QINLOCK (ripretinib) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft QINLOCK (ripretinib) PPI received on December 13, 2019 and received by DMPP and OPDP on April 17, 2020.
- Draft QINLOCK (ripretinib) Prescribing Information (PI) received on December 13, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 17, 2020.

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. In our review of the PPI the target reading level is at or below an 8th grade level.

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)

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.

5 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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

/s/

SHAWNA L HUTCHINS
04/24/2020 01:31:10 PM

ROBERT L NGUYEN
04/24/2020 01:33:23 PM

LASHAWN M GRIFFITHS
04/24/2020 02:36:33 PM

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:	April 13, 2020
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	NDA 213973
Product Name and Strength:	Qinlock (ripretinib) tablets, 50 mg
Applicant/Sponsor Name:	Deciphera Pharmaceuticals LLC (Deciphera)
OSE RCM #:	2019-2213-1
DMEPA Safety Evaluator:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on April 8, 2020 for Qinlock. The Division of Oncology 3 (DO3) requested that we review the revised container labels and carton labeling for Qinlock (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]

2 CONCLUSION

The Applicant implemented all of our recommendations, as well as proposed the following changes to the container labels and carton labeling:

- Added trademark statement to carton labels only: "QINLOCK™ is a trademark of Deciphera Pharmaceuticals, LLC"
- Revised tradename in web address to be all uppercase: "www.QINLOCK.com"
- To further differentiate the professional sample from the commercial product, "Not for Sale" was updated (b) (4).
- Revised the color of the net quantity on the carton and bottle label of the professional sample (30) (b) (4)

[a] Thomas S. Label and Labeling Review for Qinlock (NDA 213973). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MARCH 20. RCM No.: 2019-2213.

We find these additional changes acceptable from a medication safety perspective, and we have no additional recommendations at this time.

3 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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

/s/

SARAH E THOMAS
04/13/2020 07:18:23 PM

CHI-MING TU
04/14/2020 12:31:19 PM

Clinical Inspection Summary

Date	4/6/2020
From	Michele Fedowitz, M.D. Yang-Min (Max) Ning, MD, PhD. Kassa Ayalew, M.D., M.P.H. Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Leslie Doros M.D. Margaret Thompson M.D. Ashley Ward M.D. Leah Her, RPM 'Lola Fashoyin-Aje M.D., M.P.H. Division of Oncology 3 (DO3) Office of Oncologic Diseases (OOD)
NDA#	213973
Applicant	Deciphera Pharmaceuticals, LLC
Drug	Ripretinib (QINLOCK)
NME (Yes/No)	Yes
Therapeutic Classification	Kinase inhibitor
Proposed Indication(s)	Ripretinib is a kinase inhibitor indicated for the treatment of patients with advanced gastrointestinal stromal tumor (GIST) who have received (b) (4).
Consultation Request Date	12/13//2019
Summary Goal Date	4/13/2020
Action Goal Date	6/12/2020
PDUFA Date	6/13/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical data from a randomized, placebo-controlled trial (Study DCC-2618-03-001) was submitted to the Agency in support of an original New Drug Application (NDA 213973) for ripretinib for use in patients with advanced gastrointestinal stromal tumor (GIST). The study sponsor, Deciphera Pharmaceuticals, and 3 participating clinical investigators of the study, Dr. Rodolfo Bordoni (Site 104), Dr. Scott Okuno (Site 116), and Dr. Cesar Serano (Site 601) were selected for audit.

The inspections of the three investigator sites and the study sponsor revealed no significant objectionable findings related to the data integrity or human subject protection in the conduct of Study DCC-2618-03-001. There was no evidence of underreporting of significant or

unexpected adverse events. Based on these inspection results, the data generated by the inspected clinical sites, submitted by the Applicant, appears to be acceptable in support of this NDA.

II. BACKGROUND

The Applicant has submitted clinical data from a randomized clinical trial, Study DCC-2618-03-001, to support the following indication: QINLOCK (ripretinib) is a kinase inhibitor indicated for the treatment of patients with advanced gastrointestinal stromal tumor (GIST) who have received (b) (4).

Study DCC-2618-03-001 (NCT03353753) was a randomized (2:1), placebo-controlled, double-blind Phase 3 trial comparing the efficacy of ripretinib plus best supportive care to placebo plus best supportive care in patients with advanced GIST who had received at least 3 prior anticancer therapies (imatinib, sunitinib, and regorafenib). The primary efficacy measure was progression-free survival (PFS) as assessed by blinded independent central review (BICR) using modified RECIST 1.1 criteria as specified in the protocol. Supportive efficacy measures included objective response rate (ORR) by BICR and overall survival (OS).

From February 27, 2018 through May 31, 2019 (data cut-off date for the interim efficacy analysis), 129 subjects were enrolled, with 85 assigned randomly to the ripretinib arm and 44 to the placebo arm. The subjects were recruited from 29 study sites in 12 countries, including Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Poland, Singapore, Spain, United Kingdom, and the United States (U.S.). Of the enrolled subjects, 46% were from the U.S. This study was ongoing as of the data cut-off date.

For clinical inspection, the review division, DO3, and OSI selected three clinical investigators (CI): Rodolfo Bordoni (Site 104), Scott Okuno (Site 116), and Cesar Serano (Site 601). The three sites had relatively high enrollments of subjects. Site 601 had the highest enrollment, accounting for 11% of subjects in the efficacy-evaluable population and had the highest weighted treatment effect in favor of subjects on the ripretinib arm. Site 104 also had a high weighted treatment effect and a high number of serious adverse events (SAEs) reported. Site 116 had the highest treatment responders reported. None of the three clinical investigators had previously been inspected.

Inspection of the study sponsor, Deciphera Pharmaceuticals, LLC, was also requested given this new molecular entity application. The firm had no FDA inspection history prior to this application.

III. RESULTS (by site):

1. Rodolfo Bordoni, Clinical Site 104
Northside Hospital Cancer Center 1000 Johnson Ferry Road, NE
Atlanta, GA 30342

This CI was inspected between February 18 and February 21, 2020 as a data audit for the study DCC-2618-03-001. This was the first FDA inspection for this investigator. There were 7 subjects consented at the site and all 7 were enrolled into the study: 4 on the ripretinib arm and 3 on the placebo arm. At the time of data cutoff, 5 subjects had discontinued study treatment: four (4) due to progressive disease (Subjects (b) (6)) and one due to an adverse event (Subject (b) (6)). Two subjects (Subjects (b) (6) (b) (6)) remained on treatment.

The inspection reviewed source records for all enrolled subjects, which included, but were not limited to, the informed consent forms (ICFs), eligibility, and subject clinical reports (e.g., ECG, ECOG scores, medical progress notes, adverse events, study medication compliance, and laboratory results). The data listings submitted for this site in the NDA were examined by comparison with the source data at the site.

The inspection included a review of documents related to the sites IRB approval and correspondences, drug accountability records, financial disclosure documents, training records, and the monitoring plan and site visit log.

The inspection revealed no significant deficiencies, with no Form FDA 483 issued to the investigator. The primary endpoint data was verifiable and there was no evidence of under-reporting of AEs or protocol violations.

2. Scott Okuno, Clinical Site 116
Mayo Clinic Cancer Center 200 First Street SW
Rochester, MN 55905

This CI was inspected between February 25 and February 28, 2020 as a data audit for the study DCC-2618-03-001. This was the first FDA inspection for this investigator. The site screened 5 subjects and enrolled all the 5 into the study. The site also accepted two (Subjects (b) (6) (b) (6)) transferred from (b) (4) (Site 112). Of the 7 subjects, 5 were on the ripretinib arm and 2 on the placebo arm. As of the data cutoff date, three subjects were discontinued from study treatment two (Subjects (b) (6)) due to death and one (Subject (b) (6)) due to progressive disease. Four subjects remained on study treatment (Subjects (b) (6)).

A comprehensive review of source records of all the 7 subjects included, but was not limited to, the informed consent forms, subject medical records, physician written orders and progress notes, subject study visit records and concomitant medications, and adverse events and serious adverse events. The Applicant's data listings submitted for this site were examined by comparison with source data at the site. The inspection also reviewed documents related to the

study protocol, Institutional Review Board) (IRB) correspondence, site reporting to the sponsor and IRB, drug receipt, storage, shipment, tracking and accountability records; sample collection and handling, and shipment, curriculum vitae of the Clinical Investigator (CI) and Sub-Investigators, monitoring correspondence, and a list of studies conducted by the CI in the last three years.

The inspection reported that the primary endpoint data was verifiable with source records and that there was no evidence of under-reporting of significant AEs or protocol violations.

The inspection also identified several non-compliance findings, leading to a Form FDA 483 issued at the end of the inspection. The cited Observation was “the investigation was not conducted in accordance with the signed statement of investigator and investigational plan”.

Specifically, the following protocol requirements were not followed:

(b) (4)

(b) (4)

Reviewer's Comments:

(b) (6)

assessments. Further, the CI is also implementing a preventative action plan to mitigate the risk of reoccurrence of these deviations. The plan appears comprehensive and acceptable.

3. Cesar Serano, Clinical Site 601
Hospital Universitari Vall d'Hebrón
Passeig Vall d'Hebron 119-129
Barcelona, 8035

This foreign CI was inspected between February 17 and February 21, 2020 as a data audit for the study DCC-2618-03-001. This was the first FDA inspection for this investigator. The site screened 14 subjects and enrolled 14 of them, with 10 on the ripretinib arm and 4 on the placebo arm. As of the data cut-off, 8 subjects died ((b) (6) (b) (6)), 3 came off treatment secondary to progressive disease ((b) (6)), and 3 actively on study treatment (b) (6). After the data cutoff, Subject (b) (6) had evidence of progressive disease and was discontinued of study treatment.

Source records were reviewed for all 14 subjects and compared with the data listings submitted by the sponsor for the site. The reviewed records included, but were not limited to, subjects' records (clinical source data, subject paper diaries, laboratory results, adverse events). The data listings submitted in the NDA were examined by comparison with source data at the site. Regulatory documents related to the conduct and oversight of this study were also reviewed in this inspection.

The primary endpoint data was verifiable. There were 2 subjects who had adverse events found in the source data but not in the submitted data listings. These are summarized below.

Subject (b) (6): on (b) (6), this subject had an asymptomatic thrombus detected superior vena cava (IVC) in a radiographic scan. The investigator prescribed heparin and documented this AE and treatment with heparin but did not enter the event until 1/18/2019.

Subject (b) (6) had an AE nausea which was documented in the source on 8/27/2018 and

deemed as related to a new concomitant medication (tramadol). This was not found in data listings. The investigator did not believe this AE was clinically relevant to study treatment but rather to tramadol.

Besides these two AEs, there was no evidence of under-reporting of significant AEs or protocol violations.

***Reviewer's Comments**:*
For Subject (b) (6)*, all other adverse events were reported. This missed reporting of asymptomatic radiological finding appears to be isolated. For patient* (b) (6)*, the CI did document "nausea" in the source but did not report it as an AE. Of note, nausea has been included in the Investigator's brochure as a common treatment-emergent AE.*

4. Deciphera Pharmaceuticals, LLC, Sponsor
200 Smith Street
Waltham, MA 02451
Phone: 781-209-6400

The inspection of this study sponsor was performed on January 28, 2020 through February 6, 2020 to evaluate the sponsor's conduct and management of the study DCC-2618-03-001. This was the first FDA inspection for this sponsor.

The inspection covered sponsor's responsibilities for the investigation of ripretinib and focused on sponsor's oversight of the vendors and/clinical research organizations (CROs) used for important functions of the inspected study. Four clinical investigators (Sites 102, 104, 114, and 116) were also evaluated during the inspection for site monitoring, data reporting, and record review. Source documents reviewed during the inspection included but were not limited to organizational charts, Standard Operating Procedures, Master Service Agreements (MSAs), Clinical Operations Plans, Study Blinding Plan, Monitoring Plans, Sponsor's audit plans and audit reports, site selection and monitoring plans, site monitoring reports, correspondence between the sponsor and clinical sites and CROs/vendors, training records, FDA 1572s, financial disclosure forms, electronic case report forms (eCRFs), protocol deviations, meeting minutes, adverse event reporting, and investigational product accountability records.

The inspection found no significant deficiencies and no Form FDA-483 was issued at the end of the inspection. The sponsor appeared to maintain adequate oversight and documentation of Study DCC-2618-03-001. There was no evidence of blinded personnel being unblinded prior to the protocol-specified unblinding. Data collection and data validation for the study were found to be satisfactorily managed at the sponsor's site.

***Reviewer's Comments:** After the Sponsor site inspection was completed, a complaint to CDER-OSI-GCP was received, claiming improper unblinding of study personnel at Deciphera had occurred. Specifically, the complaint stated, "Per the blinding plan, 'only one person at Deciphera should have had access to the blinded data', but up to six (6) Deciphera employees had access to the blinded data."*

As mentioned, the Blinding Plan and oversight of the blinding process were reviewed during the inspection. The Blinding Plan (version 4.0) was reviewed, which allowed for more than one Sponsor personnel to be unblinded under certain circumstances. It states, "Only a single Sponsor representative has access to the randomization codes, and this is for the purposes of distribution of clinical drug supply. Select Sponsor representatives will be unblinded to individual patient treatment assignments and this will only occur once a patient has confirmed radiographic progression by independent review" (Page 6). In addition, the Protocol for DCC-2618-03 (amendment 5) allowed unblinding for emergency and safety related reporting. Specifically, it states: "Vendors responsible for pharmacovigilance and regulatory personnel at the Sponsor to satisfy serious adverse event (SAE) processing and reporting regulations" (page 53 of 97).

The sponsor reported no emergency and/or accidental unblinding occurred to date. The list of unblinded Sponsor personnel in Appendix 1 of the Blinding Plan (version 4.0) is found to be consistent with information contained in the inspection collected list "Deciphera User Access to Vendor System". Besides the Sponsor personnel with access to the IRT for the purposes of dispensing the clinical drug supply, there are six other Sponsor personnel unblinded for the purposes of either pharmacovigilance and SAE review or disease progression unblinding (unblinding occurring when disease progression is confirmed by independent central review). Given that there were unblinded vendor personnel, the correspondence between unblinded vendors and Deciphera was examined during the inspection and there was no communication identified between blinded and unblinded personnel.

In summary, the evidence collected from this inspection does not seem to support the post-inspection complaint received by OSI, but rather showed the Sponsor's adherence to the Blinding Plan and Protocol. Of note, the primary endpoint data that relied on independent central review for this study is unlikely to be affected by unblinding issues.

{See appended electronic signature page}

Michele B. Fedowitz, MD.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Max,
Acting Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm.
Review Division /Division Director/
Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
OSI/DCCE/GCP Reviewer/
OSI/ GCP Program Analysts/
OSI/Database PM/Dana Walters

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

/s/

MICHELE B FEDOWITZ
04/06/2020 10:54:34 AM

YANGMIN NING
04/06/2020 11:05:29 AM

KASSA AYALEW
04/06/2020 11:36:01 AM

Interdisciplinary Review Team for Cardiac Safety Studies

Consultation Review

Submission	NDA 213973
Submission Number	006
Submission Date	12/13/2019
Date Consult Received	12/30/2019
Drug Name	Ripretinib
Indication	treatment of patients with advanced gastrointestinal stromal tumors (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib
Therapeutic dose	150 mg once daily (QD)
Clinical Division	DO3

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

This review responds to your consult dated 12/30/2019 regarding the sponsor's QT assessment. We reviewed the following materials:

- Previous IRT review under IND 125279 dated 09/27/2019 in DARRTS;
- Study dcc-2618-01-001 report (Submission 0002);
- Study dcc-2618-01-001 cardiac safety report (Submission 0006);
- Sponsor's response to Information Request (Submission 0013);
- Proposed label (Submission 0006); and
- Summary of clinical pharmacology (Submission 0006).

1 SUMMARY

No large mean increases in the QTc interval (i.e., >20 msec) were observed for the therapeutic dose of 150 mg QD ripretinib. In the absence of a positive control or a large exposure margin above therapeutic exposures, there is reluctance to draw conclusions of lack of a QT effect for ripretinib.

The effect of ripretinib was evaluated in the dose-ranging study DCC-2618-01-001. The data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that ripretinib is associated with large mean increases in the QTc interval (refer to section 4.5) – see Table 1 for overall results. The findings of this analysis are further supported by trends observed in the by-time analysis (section 4.3) and the categorical analysis (section 4.4).

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

ECG parameter	Treatment	Concentration	ΔQTcF	90% CI
QTc	Ripretinib 150 mg QD	857.1	-6.9	(-10.5, -3.3)

For further details on the FDA analysis please see section 4.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to Submission 0006 from the IRT. Our changes are highlighted (addition, ~~deletion~~). Our edits are for suggestions only and we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology (b) (4) no large mean increases in (b) (4) QTc interval (i.e. > 20 ms) was (b) (4).
The study design does not support an evaluation (b) (4) (b) (4) *on the QT/QTc interval. Therefore, we propose to specify the extent of QT evaluation in the label.*

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Ripretinib (also known as DCC-2618 or (b) (4)) is a kinase inhibitor indicated for the treatment of patients with advanced gastrointestinal stromal tumor (GIST) who have received (b) (4). The recommended dose is 150 mg QD. Ripretinib and its major active metabolite (DP-5439) are the predominant component in systemic circulation. CYP3A4/5 is the major metabolizer of ripretinib and DP-5439. Renal elimination does not play an important role in the excretion of ripretinib and DP-5439. The highest exposure scenario has not been identified (e.g. hepatic impairment study ongoing). At the time of this review, the maximum increase on ripretinib exposure is 2-fold on AUC and 136% in Cmax (CYP3A4 inhibitor; less effect on DP-5439). High-fat meal increases ripretinib exposure by 22% (Cmax) and 30% (AUC), and DP-5439 exposure by 66% (Cmax) and 47% (AUC), after a single 150 mg dose.

We reviewed the QT assessment proposal previously under IND 125279 (DARRTS 09/27/2019) and concluded that the concentration-QTc analysis based on study DCC-2618-01-001 appeared reasonable to characterize the effect of ripretinib on the QT/QTc interval at the 150 mg QD dose. Whether the data would be adequate to exclude large

mean increase (i.e. >20 ms) would be a review issue. The IRT requested the following information to be included in the concentration-QTc analysis report:

a) the number of subjects at each dose level and in each study cohort;
b) the ECG sampling schedule relative to last dose in the dose expansion cohort; and
c) justification for pooling data from the dose escalation and dose expansion cohorts in the presence of differences in ECG acquisition and baseline selection.

In the current submission, the sponsor provided a cardiac safety report for study DCC-2618-01-001. This is a multicenter, Phase 1, open-label, escalation/expansion study in patients with advanced malignancies. Initially the study included a food effect portion (a single dose after high-fat meal on Day -7, and fasted condition [1 hour before and at least 2 hours after a meal] on Cycle 1 Day 1 [C1D1]), which was removed after sufficient information was collected. Otherwise the study did not have restriction with regard to meal. According to the sponsor, continuous Holter 12-lead ECG data extraction occurred at screening; predose, 0.5, 1, 2, 4, 6, 8, 10-12, and 24 hours post dose on Day -7 (if applicable) and C1D1; predose on C1D8; predose, 0.5, 1, 2, 4, 6, 8, 10-12 hours post dose on C1D15; predose on C1D22; predose and 2 hour post dose on C2Dl; predose on Day 1 of any additional cycles; End of Study; and Unscheduled visits. 7 patients in the expansion phase also received Holter monitoring.

In this QT assessment report, the primary analysis is concentration-QTc analysis for all time points on Day -7 in Cycle 1. The primary endpoint was QTcF. The proposed therapeutic dose remains the same. 59 patients (52 from the escalation phase and 7 from the expansion phase) who had Holter measurements at baseline and at least 1 time point postdose with a valid change-from-baseline QTcF value were included in the analysis. Patients in the food effect group used predose ECG on Day -7 as the baseline; otherwise, predose ECG on C1D1 was used. Patient disposition is as follows:

20 mg BID	30 mg BID	50 mg QD	50 mg BID	100 mg QD
3	3	1	6	5
100 mg BID	150 mg QD	150 mg BID	200 mg BID	250 mg QD
10	18	4	3	6

3.1.2 Nonclinical Safety Pharmacology Assessments

The Predictor™ hERG Fluorescence Polarization Assay by Invitrogen was used to assess hERG channel binding potential in a homogenous, fluorescence polarization-based format. The average hERG IC50/concentration required to achieve 20% inhibition (IC20) values were 7.9 μM/2.0 μM for ripretinib and 2.5 μM/0.41 μM for DP-5439.

3.2 SPONSOR'S RESULTS

3.2.1 By Time Analysis

The primary analysis for ripretinib was based on exposure response analysis. Please see section 3.2.3 for additional details.

Reviewer's comment: *The sponsor performed by-time analysis using linear model. However, due to the small sample size, the by-time analysis is not interpretable. The*

FDA statistical reviewer used non-parametric method in by-time point analysis to explore the time trend of data. Please see section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTcF (i.e., > 500 msec or ΔQTcF > 60 msec) .

Reviewer's comment: *Review's results are similar. Please see section 4.4 for reviewer's additional details.*

3.2.3 Exposure-Response Analysis

The sponsor used the linear mixed effect model using time-matched concentration of ripretinib as a covariate, centered baseline QTcF as an additional covariate, and subject as a random effect for both intercept and slope. A similar analysis was conducted using DP-5439 plasma concentration as the exposure metrics. The results of the sponsor's analyses show an absence of large mean increase on the QT/QTc interval.

Reviewer's comment: *The reviewer's analysis gives similar results.*

3.2.4 Cardiac Safety Analysis

In the study population of patients with advanced malignancies, there were 28 AEs leading to death. Two deaths were cardiac-related: one cardiac arrest and one myocardial infarction. There were 3 sudden deaths. Fifteen patients experienced Grade 3/4 hypertension. None of the patients reported arrhythmias.

Four patients had Grade 3 syncope, but there was no evidence of QTc prolongation in the patient narratives.

Two patients had seizures. Both patients (b) (6) (b) (6) had Stage IV glioblastoma and the investigator deemed the seizures were not related to study medication.

There were no TEAEs of QTc prolongation Grade 2 or greater.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e. |median| < 10 bpm) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment

Not applicable.

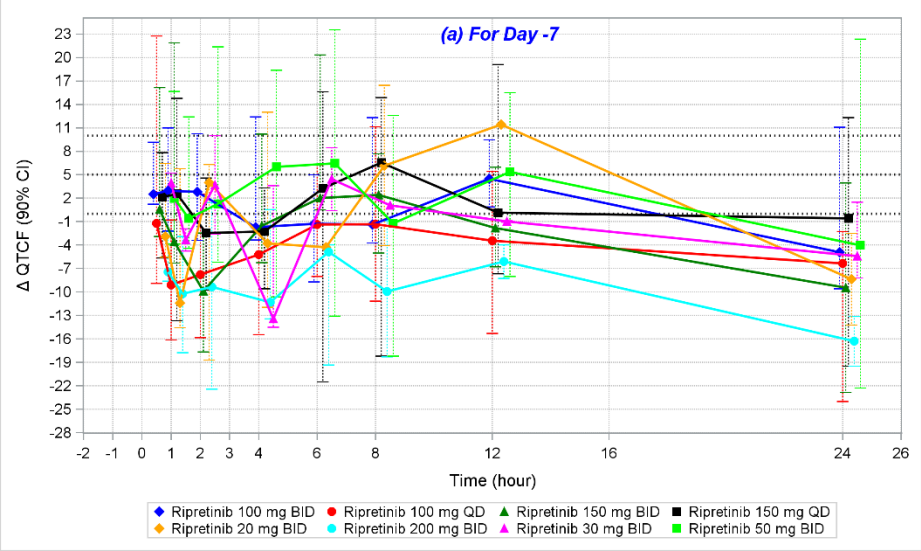
4.3 BY-TIME ANALYSIS

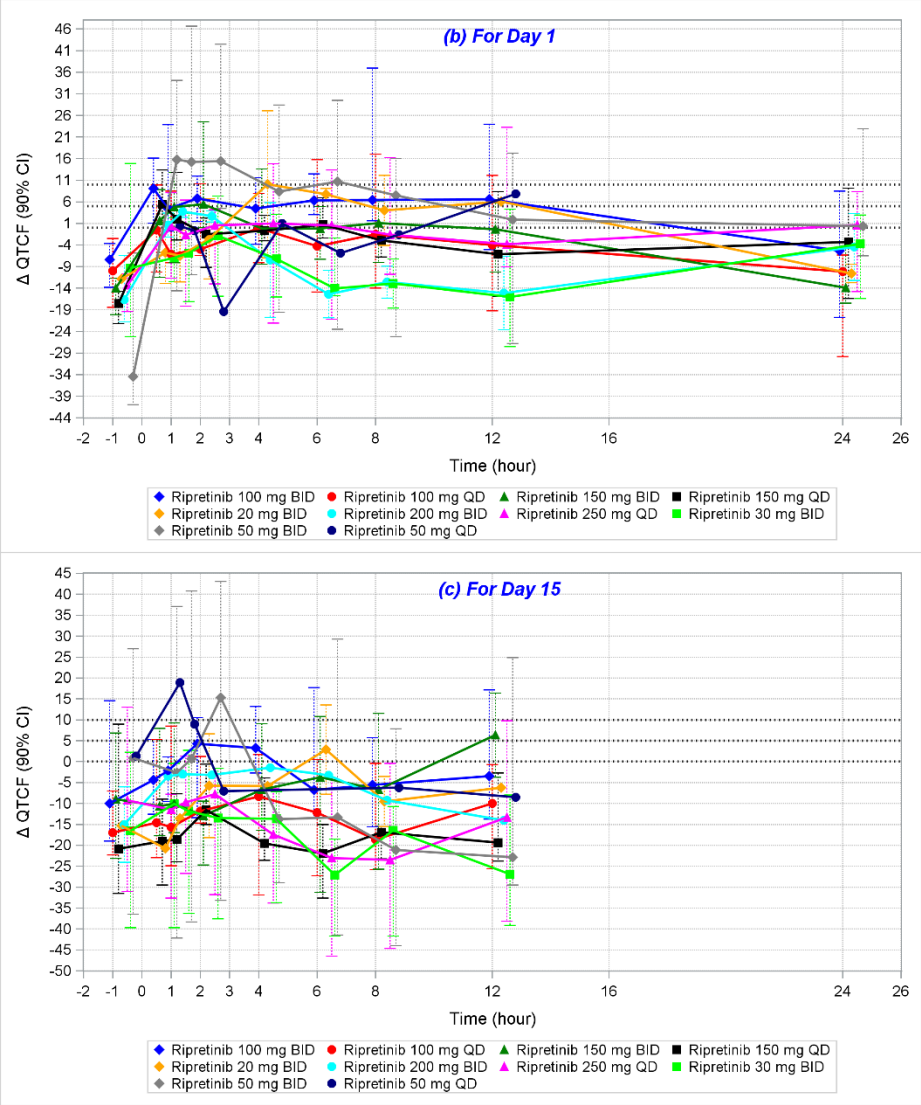
The analysis population used for the by-time analysis included all subjects with a baseline and at least one post-dose ECG. The statistical reviewer evaluated the ΔQTcF effect using nonparametric descriptive statistics.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for different treatment groups. Given the small sample size within each dose cohort, the non-parametric analysis results (which was not powered as primary analysis in the original study design) may not be interpretable.

Figure 1: Median and 90% CI of ΔQTcF Time Course (unadjusted CIs).





Reviewer's comment: *In general, for Ripretinib 150 mg QD dose group, there are no apparent time trends in post-baseline medians of ΔQTcF on Day -7 and Day 1 (negative and positive values across different timepoints); the post-baseline medians of ΔQTcF tended to be negative on Day 15.*

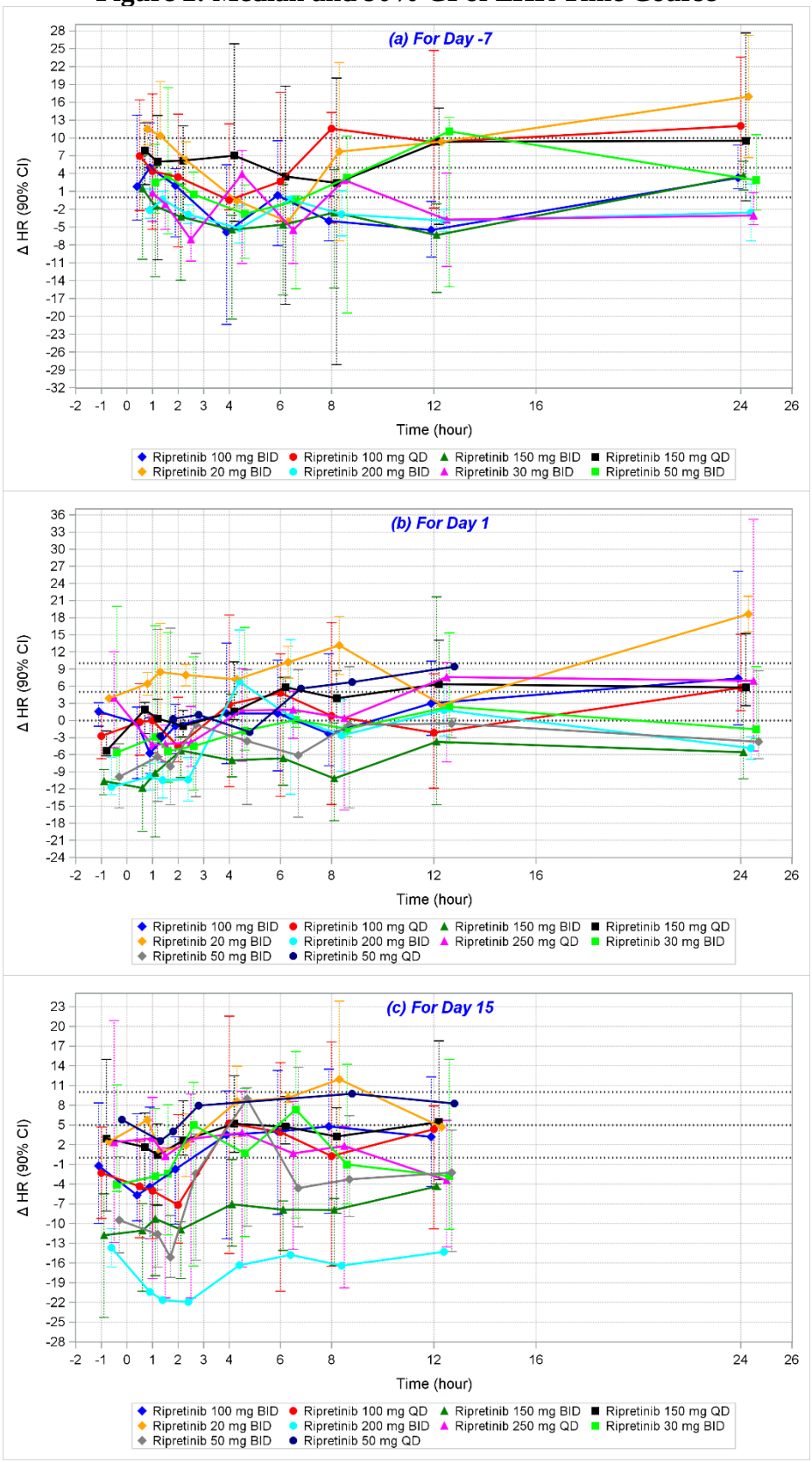
4.3.1.1 Assay sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔHR for different treatment groups

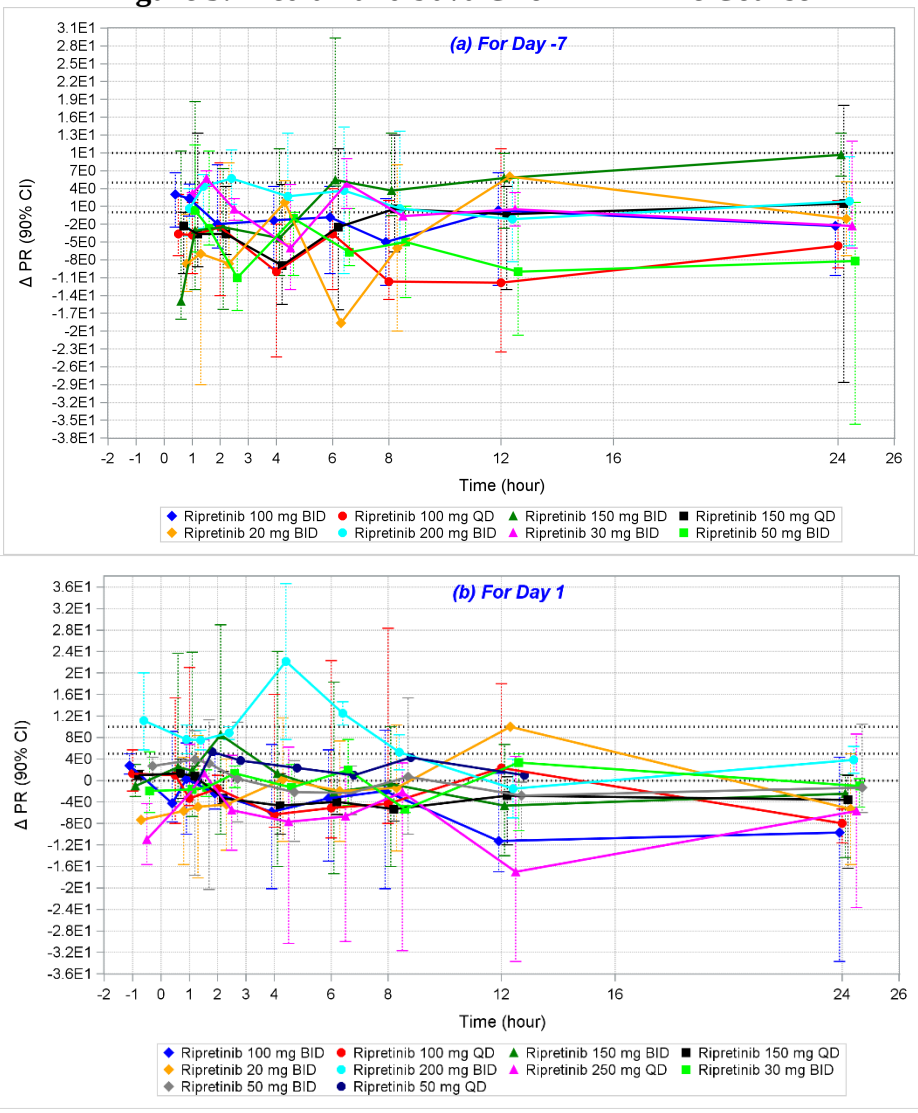
Figure 2: Median and 90% CI of ΔHR Time Course

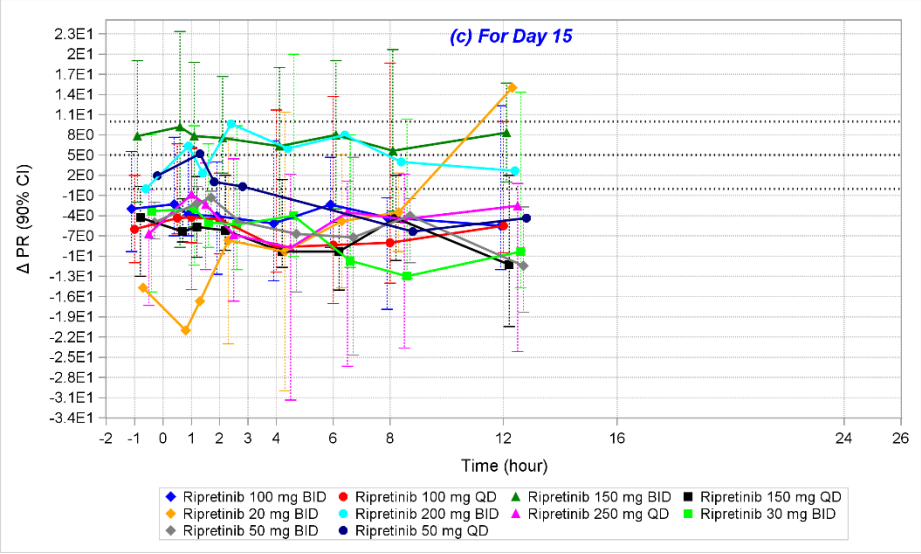


4.3.3 PR

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

Figure 3: Median and 90% CI of ΔPR Time Course

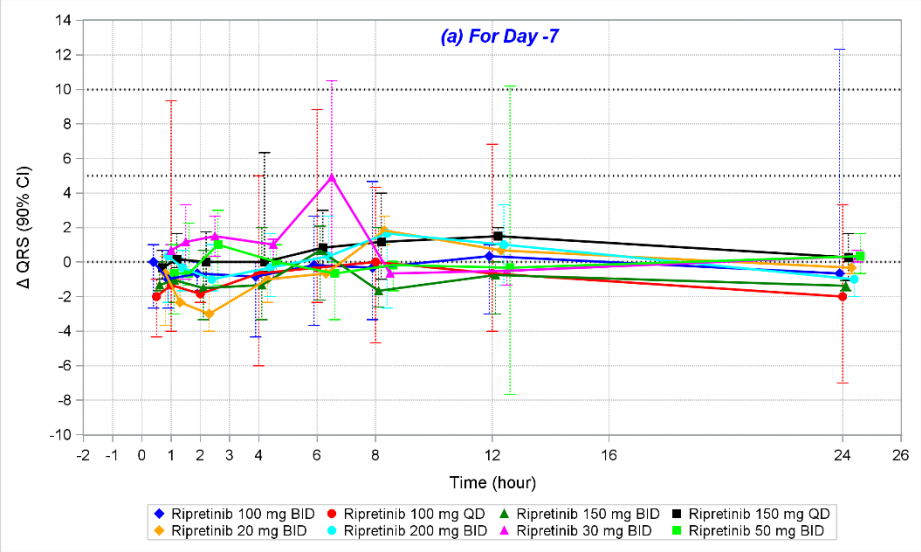


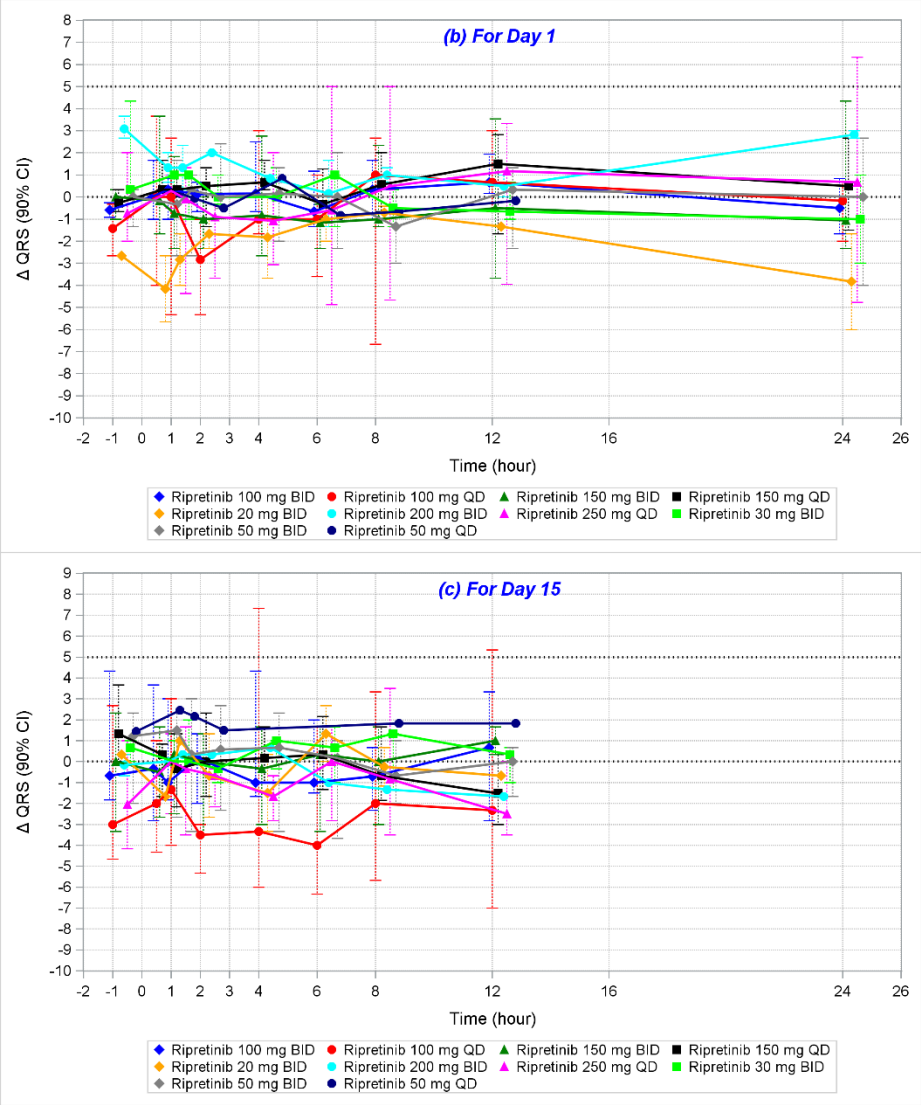


4.3.4 QRS

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

Figure 4: Median and 90% CI of ΔQRS Time Course





4.4 CATEGORICAL ANALYSIS

Categorical analysis were 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 and includes both scheduled and unscheduled ECGs.

4.4.1 QTc

No subject had QTcF>500 msec or ΔQTcF >60 msec.

4.4.2 HR

Table 2 lists the categorical analysis results for maximum HR (<100 bpm and >100 bpm). There are 5 subjects experienced HR>100 bpm. One subject experienced HR>100bpm and also had a maximum HR increase from baseline of 37%

Table 2: Categorical Analysis for HR (maximum)

Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
59	1447	54 (91.5%)	1415 (97.8%)	5 (8.5%)	32 (2.2%)

4.4.3 PR

There are no subjects with a PR interval above 220 msec with 25% increase over baseline.

4.4.4 QRS

Table 3 lists the categorical analysis results for QRS (less than 120 msec and above 120 msec with and without 25% increase over baseline). One subject had a QRS value > 120 msec with increase over baseline 25.2%.

Table 3: Categorical Analysis for QRS

Total (N)		Value <= 120 msec		Value > 120 msec & < 25%		Value > 120 msec & >= 25%	
# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
59	1447	51 (86.4%)	1368 (94.5%)	7 (11.9%)	77 (5.3%)	1 (1.7%)	2 (0.1%)

4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK on Day -7 and in Cycle 1. Because high fat meal does not have substantial effect on ripretinib PK and majority of the study data come from the study portions without constraint with regard to food, the reviewer agrees with the sponsor's proposal to include Day -7 data in the analysis.

4.5.1 QTc

Prior to evaluating the relationship between drug-concentration and QTc using a linear model, the three key assumptions of the model needs to be 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 ΔΔQTc and 3) presence of non-linear relationship.

Figure 2 shows the time-course of ΔHR, which shows an absence of significant ΔHR changes across different dose groups and between study days. Figure 5 evaluates the time-course of drug-concentration and ΔQTcF at the 150 mg QD dose level. The ΔQTcF profiles on Days -7 and Cycle 1 Day 1 were relatively flat without any trend of changing QTcF with changing drug exposure, and therefore the figure does not appear to show significant hysteresis with either ripretinib or DP5439 concentration. Data from the other dose groups were not shown because of the small sample size and large variability in the observations. Figure 6 shows the relationship between drug concentration and ΔQTc and supports the use of a linear model.

Figure 5: Time course of drug concentration (top) and QTc (bottom)

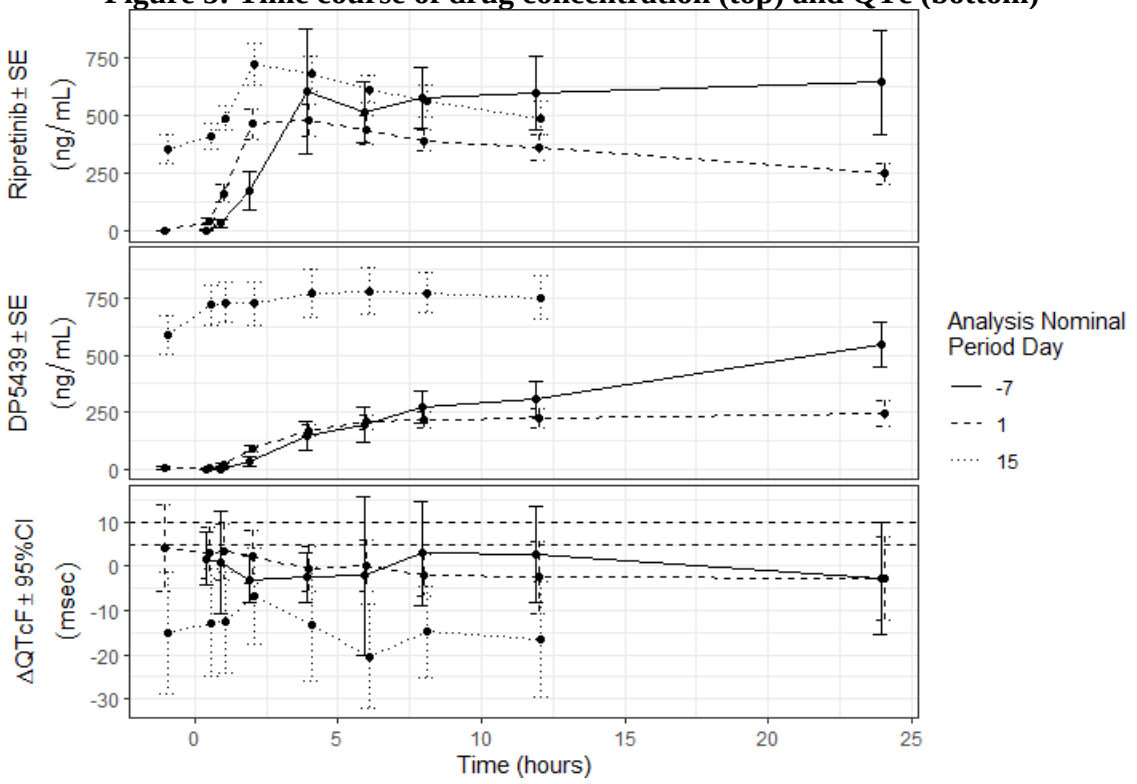
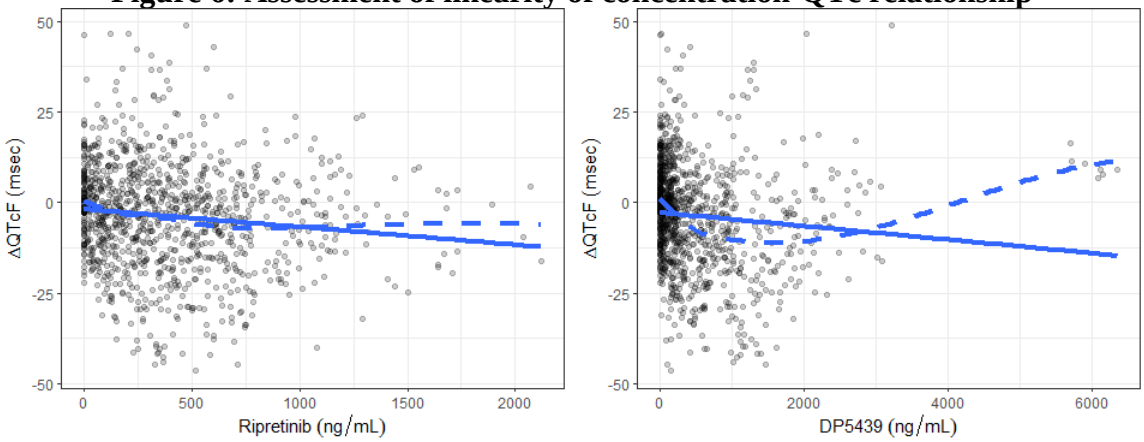


Figure 6: Assessment of linearity of concentration-QTc relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot for the ripretinib concentration-QTc model is shown in Figure 7. Predictions from the concentration-QTc model are provide in Table 4.

Figure 7: Goodness-of-fit plot for QTc

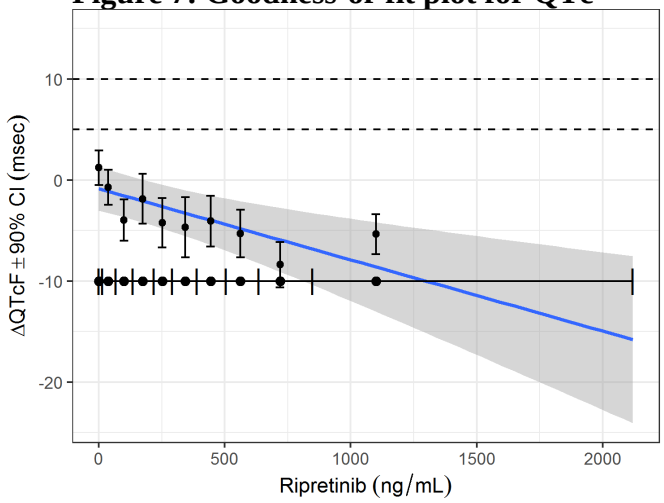


Table 4: Predictions from concentration-QTc model

Actual Treatment	Ripretinib (ng/mL)	ΔQTcF (msec)	90.0% CI (msec)
Ripretinib 20 mg BID	146.1	-1.9	(-4.0 to 0.2)
Ripretinib 30 mg BID	463.6	-4.1	(-6.6 to -1.6)
Ripretinib 100 mg QD	617.9	-5.2	(-8.1 to -2.3)
Ripretinib 50 mg BID	710.0	-5.8	(-9.0 to -2.7)
Ripretinib 50 mg QD	742.0	-6.1	(-9.3 to -2.8)
Ripretinib 150 mg QD	857.1	-6.9	(-10.5 to -3.3)
Ripretinib 100 mg BID	974.6	-7.7	(-11.7 to -3.7)
Ripretinib 250 mg QD	1,148.6	-8.9	(-13.5 to -4.3)
Ripretinib 150 mg BID	1,219.3	-9.4	(-14.3 to -4.6)
Ripretinib 200 mg BID	1,473.1	-11.2	(-17.0 to -5.4)

An analysis using DP5439 concentration as the exposure metrics yields similar findings (results not shown).

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

/s/

NAN ZHENG
03/24/2020 02:21:09 PM

YU YI HSU
03/24/2020 02:23:55 PM

DALONG HUANG
03/24/2020 02:31:13 PM

MICHAEL Y LI
03/24/2020 02:32:26 PM

LARS JOHANNESEN
03/24/2020 02:34:27 PM

CHRISTINE E GARNETT
03/24/2020 02:36:57 PM

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

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

Date of This Review:	March 20, 2020
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	NDA 213973
Product Name, Dosage Form, and Strength:	Ripretinib tablets, 50 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Deciphera Pharmaceuticals LLC (Deciphera)
FDA Received Date:	November 19, 2019
OSE RCM #:	2019-2213
DMEPA Safety Evaluator:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As a part of the NDA review process, this review evaluates the proposed ripretinib tablets container labels, carton labeling, prescribing information (PI), and patient information for areas of vulnerability that could 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 Label and Labeling 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

The proposed labels and labeling provide instructions to store ripretinib tablets in the original container. We communicated with the review team via email on February 4, 2020 to clarify the intended meaning of the storage instructions (e.g., dispense to patients in original manufacturer container bottle versus retain in original packaging until dispensing). OPQ clarified via email on February 4, 2020 that the product is prone to hydrolysis under elevated temperature and humidity conditions. Also, all stability batch bottles contain desiccant, and so it is unknown how the product behaves without the desiccant. Therefore, OPQ recommends that the product should be dispensed to patients in the original container that contains the desiccant.

We considered that it may be necessary for pharmacies to dispense a quantity less than a full bottle (e.g., cash payers, vacation supply, or an emergency supply until patients can see the doctor for a new prescription). Furthermore, hospital pharmacies may repackage ripretinib tablets into unit-dose blister packs because drugs are routinely dispensed in unit-doses in the usual hospital setting. We asked the Review Team to consider asking the Applicant to supply ripretinib in unit-dose blister packs to ensure the safe and effective use of this product, and

that in order to not hold up treatment options for oncology patients ripretinib unit-dose blister packs may be introduced after approval of this NDA. The Review Team anticipates that the proposed product will be used as fourth line therapy primarily in the outpatient setting, with predicted rare use in the inpatient hospital setting. Therefore, the review team decided to not pursue a unit-dose blister packaging. Based on this reasoning and the fact that the current proposed packaging configuration of 90-count tablet bottles will facilitate all doses in the labeling, we find this approach acceptable from a medication safety perspective.

Our review of the proposed container labels, carton labeling, PI, and patient information identified areas where the labels and labeling may be improved to promote the safe use of the product. Thus, we provide related recommendations below in Section 4.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed PI, patient information, container labels and carton labeling for ripretinib may be improved to promote the safe use of the product as described in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 3 (DO3)

A. Prescribing Information

1. Replace the proprietary name Qinlock*** with a TRADENAME placeholder for now (e.g., TRADENAME) on all labels and labeling, as the proposed proprietary name was found unacceptable on March 9, 2020.[a]
2. Dosage and Administration Section, Highlights
    a. We note that information related to dose modifications for adverse reactions is missing from the Highlights Dosage and Administration Section. We recommend adding the following statement in this section to alert users to additional dosing information provided in the full PI: "Dosage modification is recommended in patients experiencing certain adverse reactions (2.2)."
3. Dosage and Administration Section, Full PI
    a. In Table 2, clarify the purpose of the first bullet in the Hypertension Grade 3 section. The second bullet seems to define the first step in dose adjustment for Grade 3 hypertension and incorporates the first bullet.
4. How Supplied/Storage and Handling Section
    a. Consider providing information about child resistant packaging (CRP) and specify the CRP package.[b]

---

[a] Harris, D. FDA Communication: Proprietary Name Request Unacceptable for Qinlock***. Silver Spring (MD): FDA, CDER, OND, DO3 (US); 2020 MARCH 09. IND 125279 and NDA 213973.

[b] Draft Guidance for Industry: Child-Resistant Packaging Statements in Drug Product Labeling. 2017. Available from: https://www.fda.gov/media/106673/download.

b. Revise the statement "Store in original container…" to "Dispense to patient in original container only. Store in the original container with the desiccant to protect from moisture and light. Replace cap securely each time after opening. Do not discard desiccant. Store at 20°C to 25°C (68°F to 77°F); excursion permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]." to aid users in understanding why the product must be stored in the original container.

B. Patient Information

(b) (4)

4.2 RECOMMENDATIONS FOR DECIPHERA PHARMACEUTICALS LLC (DECIPHERA)

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

A. General Comments (All Container labels & Carton Labeling)

1. Add the statement "Attention: Dispense and store TRADENAME in the original container to protect from moisture and light." to the principal display panel to alert pharmacists/dispensers to dispense ripretinib tablets in the original container.
2. Revise the storage instructions on the side panel of the container labels and carton labeling to the following: "Store in the original container with the desiccant to protect from moisture and light at 20°C to 25°C (68°F to 77°F); excursion permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]."
3. Consider using a consistent color scheme to highlight the strength statement because different colors are typically used to differentiate the different strengths of a drug product. The proposed ripretinib tablets is a single-strength product of 50 mg. As currently presented, the color scheme is inconsistent (b) (4) (b) (4) for the commercial product (90 count) and (b) (4) for the professional sample (30 count).
4. Increase the prominence of the strength statement or decrease the prominence of the net quantity statement. As currently presented, the net quantity statement competes in size and prominence with the strength presentation.[c]
5. To ensure consistency with the PI, revise the usual dosage statement from (b) (4) (b) (4) to read: "Recommended Dosage: See prescribing information."

[c] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

B. Sample Container Label

1. We note the manufacturer information is immediately next to the barcode on the side panel. Revise the formatting of the manufacturing information on the side panel to provide sufficient white space around the barcode to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ripretinib received on November 19, 2019 from Deciphera Pharmaceuticals LLC (Deciphera).

Table 2. Relevant Product Information for Ripretinib	
Initial Approval Date	N/A
Active Ingredient	Ripretinib
Indication	Treatment of patients with advanced gastrointestinal stromal tumor (GIST) who have received (b) (4) (b) (4)
Route of Administration	Oral
Dosage Form	tablets
Strength	50 mg
Dose and Frequency	150 mg (three 50 mg tablets) taken orally once daily. If dose modifications are required for adverse reactions, reduce the dose (b) (4) (b) (4).
How Supplied	90-count bottles
Storage	Store in the original container at 20°C to 25°C (68°F to 77°F); excursion permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]
Container Closure	Packaged with (b) (4) desiccant into white high-density polyethylene (HDPE) bottles. The bottles are closed with (b) (4) (b) (4) child-resistant closures with a (b) (4) seal (b) (4).

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,[d] along with postmarket medication error data, we reviewed the following Ripretinib labels and labeling submitted by Deciphera Pharmaceuticals LLC (Deciphera).

- Container Label received on November 19, 2019
- Carton Labeling received on November 19, 2019
- Professional Sample Container Label received on November 19, 2019
- Professional Sample Carton Labeling received on November 19, 2019
- Prescribing Information and Patient Information (Image not shown) received on November 19, 2019, available from \\cdsesub1\evsprod\nda213973\0003\m1\us\114-labeling\114a-draft-label\uspi-patient-label-qinlock.pdf

G.2 Label and Labeling Images

Container Label

(b) (4)

2 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

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

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

/s/

SARAH E THOMAS
03/20/2020 08:01:50 PM

CHI-MING TU
03/23/2020 10:00:15 AM