

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**213246Orig1s000**

**OTHER REVIEW(S)**

**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 16, 2020

To: Autumn Zack-Taylor  
**Division of Oncology II (DO2)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Morgan Walker, PharmD, MBA, CPH  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Nazia Fatima, PharmD, MBA, RAC  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): RETEVMO (selpercatinib)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 213246

Applicant: Loxo Oncology, Inc.

## 1 INTRODUCTION

On December 4, 2019, Loxo Oncology, Inc. submitted for the Agency's review an original New Drug Application (NDA) 213246 for RETEVMO (selpercatinib) capsules. The proposed indication is for the treatment of adult (b) (4) patients with:

- metastatic RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy and have progressed following platinum-based chemotherapy and an anti-PD-1 or anti-PD-L1 therapy,
- RET-mutant medullary thyroid cancer (MTC) who require systemic therapy, have progressed following prior treatment and have no acceptable alternative treatment options.

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 II (DO2) on December 13, 2019 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for RETEVMO (selpercatinib) capsules.

## 2 MATERIAL REVIEWED

- Draft RETEVMO (selpercatinib) capsules PPI received on December 4, 2019, and received by DMPP and OPDP on April 3, 2020.
- Draft RETEVMO (selpercatinib) capsules Prescribing Information (PI) received on December 4, 2019, and received by DMPP and OPDP on April 3, 2020.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> 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 APFont to make medical information more accessible for patients with vision loss.

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.

-----  
**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/  
-----

MORGAN A WALKER  
04/16/2020 12:26:07 PM

NAZIA FATIMA  
04/16/2020 03:19:19 PM

LASHAWN M GRIFFITHS  
04/16/2020 07:00:02 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 15, 2020  
**Requesting Office or Division:** Division of Oncology 2 (DO2)  
**Application Type and Number:** NDA 213246  
**Product Name and Strength:** Retevmo (selpercatinib) Capsules, 40 mg and 80 mg  
**Applicant/Sponsor Name:** Loxo Oncology, Inc.  
**OSE RCM #:** 2019-2472-1  
**DMEPA Safety Evaluator:** Janine Stewart, PharmD  
**DMEPA Team Leader:** Chi-Ming (Alice) Tu, PharmD, BCPS

---

#### 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on April 7, 2020 for Retevmo. Division of Oncology 2 (DO2) requested that we review the revised container labels for Retevmo (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>a</sup>

#### 2 CONCLUSION

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

---

<sup>a</sup> Stewart J. Label and Labeling Review for Retevmo (NDA 213246). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 02. RCM No.: 2019-2472.

-----  
**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/  
-----

JANINE A STEWART  
04/15/2020 09:39:36 AM

CHI-MING TU  
04/15/2020 09:43:39 AM

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

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

## Memorandum

**Date:** April 14, 2020

**To:** Autumn Zack-Taylor, Regulatory Project Manager  
Division of Oncology (DO2)

**From:** Nazia Fatima, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Brian Tran, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for RETEVMO® (selpercatinib) capsules, for oral use

**NDA:** 213246

---

In response to DO2's consult request dated December 13, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI) and carton and container labeling for the original NDA submission for RETEVMO® (selpercatinib) capsules, for oral use (RETEVMO).

OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DO2 (Autum Zack-Taylor) on April 3, 2020 and are provided below.

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

OPDP's has reviewed the carton and container labeling submitted by the Sponsor and has no comments.

Thank you for your consult. If you have any questions, please contact Nazia Fatima at 240-402-5041 or [Nazia.Fatima@fda.hhs.gov](mailto:Nazia.Fatima@fda.hhs.gov).

-----  
**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/  
-----

NAZIA FATIMA  
04/14/2020 05:30:17 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\*\*\***

---

<b>Date of This Review:</b>	April 2, 2020
<b>Requesting Office or Division:</b>	Division of Oncology 2 (DO2)
<b>Application Type and Number:</b>	NDA 213246
<b>Product Name, Dosage Form, and Strength:</b>	Retevmo (selpercatinib) Capsules, 40 mg and 80 mg
<b>Product Type:</b>	Single Ingredient Product
<b>Rx or OTC:</b>	Prescription (Rx)
<b>Applicant/Sponsor Name:</b>	Loxo Oncology, Inc.
<b>FDA Received Date:</b>	December 4, 2019 and March 20, 2020
<b>OSE RCM #:</b>	2019-2472
<b>DMEPA Safety Evaluator:</b>	Janine Stewart, PharmD
<b>DMEPA Team Leader:</b>	Chi-Ming (Alice) Tu, PharmD, BCPS

---

## 1 REASON FOR REVIEW

As part of the NDA review process for Retevmo (selpercatinib) Capsules, the Division of Oncology 2 (DO2) requested that we review the proposed container labels and prescribing information (PI) 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.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
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

We performed a risk assessment of the proposed PI and container labels for Retevmo to identify deficiencies that may lead to medication errors and other areas of improvement. We identified areas of the container labels that can be modified to improve the clarity of the information presented.

## 4 CONCLUSION & RECOMMENDATIONS

The proposed Retevmo PI is acceptable from a medication error perspective. The proposed container labels can be improved for consistency across labels and labeling. We provide recommendations for Loxo Oncology, Inc. in Section 4.1 below.

#### 4.1 RECOMMENDATIONS FOR LOXO ONCOLOGY, INC.

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

##### A. Container Labels

1. To ensure consistency with the Prescribing Information, revise the statement, (b) (4) to read “Recommended Dosage: See prescribing information.”
2. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.<sup>1</sup> The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product’s labeling.

<sup>1</sup>The draft guidance is available from: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Retevmo received on March 20, 2020 from Loxo Oncology, Inc..

<b>Table 2. Relevant Product Information for Retevmo</b>	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	selpercatinib
<b>Indication</b>	For the treatment of adult (b) (4) patients with: <ul style="list-style-type: none"><li>• metastatic RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy,</li><li>• RET-mutant medullary thyroid cancer (MTC) who require systemic therapy, or</li><li>• advanced RET fusion-positive thyroid cancer who require systemic therapy (b) (4)</li></ul>
<b>Route of Administration</b>	Oral
<b>Dosage Form</b>	Capsules
<b>Strength</b>	40 mg and 80 mg
<b>Dose and Frequency</b>	160 mg orally twice daily  (b) (4)
<b>How Supplied</b>	40 mg: bottle of 60 capsules 80 mg: bottle of 60 capsules and bottle of 120 capsules
<b>Storage</b>	Room temperature 20°C to 25°C (68°F to 77°F); temperature excursions between 15°C and 30°C (59°F to 86°F) are permitted [see USP Controlled Room Temperature].
<b>Container Closure</b>	The Retevmo drug product is packaged into white, HDPE bottles with closures containing an aluminum foil induction heat seal

	<p>liner (b) (4)</p> <p>The 40mg strength capsules are packaged in 75 cc bottles containing 60 capsules. The 80 mg strength capsules are packaged in 125 cc or 190 cc bottles containing 60 tablets or 120 capsules, respectively.</p>
--	--

## 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,<sup>a</sup> along with postmarket medication error data, we reviewed the following Retevmo labels and labeling submitted by Loxo Oncology, Inc..

- Container label received on March 20, 2020
- Prescribing Information (Image not shown) received on March 20, 2020, available from <\\cdsesub1\evsprod\nda213246\0503\m1\us\pp-se-us-0075-selpercatinib-pi.pdf>

---

<sup>a</sup> 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/  
-----

JANINE A STEWART  
04/02/2020 01:41:01 PM

CHI-MING TU  
04/02/2020 02:08:47 PM

## Interdisciplinary Review Team for Cardiac Safety Studies QT Consultation Review

Submission	NDA 213246
Submission Number	1
Submission Date	12/4/2019
Date Consult Received	12/13/2020
Drug Name	Selpercatinib
Indication	Treatment of <sup>(b) (4)</sup> RET-fusion-positive non-small cell lung cancer who require systemic therapy and have progressed following platinum-based chemotherapy and an anti-PD-1 or anti-PD-L1 therapy
Therapeutic dose	160 mg BID
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 12/13/2020 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous QT-IRT review for IND 133193 dated 03/20/2019 (original protocol); and 4/26/2019 (revised protocol) in DARRTS;
- Study LOXO-RET-18032 [report](#) (Submission 0001);
- Proposed [label](#) (Submission 0001);
- [Investigator's brochure](#) (IND 133193, Submission 0106); and
- [Highlights of clinical pharmacology and cardiac safety](#).

### 1 SUMMARY

Concentration-dependent QTc prolongation was detected in this TQT study. Based on the model, the mean increase in the QTc interval at the proposed dosing regimen (160 mg BID) is 10.6 msec (90% CI: 9.1, 12.1) msec.

The effect of selpercatinib on the QTc interval was evaluated in the thorough QT study LOXO-RET-18032. The data were analyzed using exposure-response analysis as the primary analysis. The highest dose tested in this study was a single dose of 640 mg. The mean C<sub>max</sub> following the 640 mg dose was 2355.5 ng/mL, which is approximately 20% lower than the therapeutic concentrations (mean C<sub>max</sub> of 2980 ng/mL). Results for the primary analysis are presented in Table 1. These findings are further supported by the available nonclinical data (section 3.1.2), 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	$\Delta\Delta QTc$	90% CI
QTc	320 mg, single dose	2024.5	7.0	6.0 - 8.0
QTc	640 mg, single dose	2355.5	8.3	7.1 - 9.4
QTc	160 mg BID	2980.0	10.6	9.1 - 12.1

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

The high exposure scenario in patients has not been determined because organ impairment studies are still ongoing. At this time, the maximum effect on selpercatinib exposure is by strong CYP3A4 inhibition (1.3-fold change in Cmax and 2.3-fold change in AUC); however, age, sex, race, food, P-gp/CYP3A4 inhibitor, proton-pump inhibitor and H2 antagonist do not result in substantial increases in selpercatinib exposure.

### 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 SDN 1 ([Application 213246 - Sequence 0001 - Annotated Draft Labeling Text](#)) from the QT-IRT. Our changes are highlighted (addition, ~~deletion~~) and we defer final labeling decisions to the Division.

<p><b>12.2 Pharmacodynamics</b></p> <p><u>Cardiac Electrophysiology</u></p> <p><u>The effect of selpercatinib on the QTc interval was evaluated in a thorough QT study in <del>in</del> healthy subjects. The largest mean increase in QTc is predicted to be 10.6 ms</u>  <del>(b) (4)</del> <u>The increase in QTc was concentration-</u>  <u>dependent.</u> <del>(b) (4)</del></p> <p><del>(b) (4)</del></p>
<p><i>We propose to report the predicted QTc increase at the therapeutic dose (Cmax: 2980 ng/mL) and the positive exposure-response relationship.</i></p>
<p><b>5.1 QTc Interval Prolongation</b></p> <p><del>(b) (4)</del></p>

### 3 SPONSOR'S SUBMISSION

#### 3.1 OVERVIEW

##### 3.1.1 Clinical

The IRT reviewed the QT assessment proposal previously (DARRTS, 03/20/2019 (original protocol) and 4/26/2019 (revised protocol). The primary objective was to evaluate the effects of therapeutic and suprathreshold exposure of seliperatinib on the QTc interval using exposure-response modelling. The IRT agreed with the proposed study design and analysis plan, but considered the adequacy of dose selection a review issue. There have been no changes in the assessment plan.

##### 3.1.2 Nonclinical Safety Pharmacology Assessments

Seliperatinib had an IC<sub>50</sub> value of 1.1 µM in the GLP hERG assay, which is approximately 7-fold higher than the maximum unbound concentration (C<sub>max</sub>(unbound) of 153 nM) at the clinical dose of 160 mg BID.

In ion channel-blocking assays, seliperatinib was found to only block hERG and had minimal to no effects on other cardiac channels.

No abnormal ECG waveforms, arrhythmias or quantitative effects on ECG and hemodynamic data were attributed to seliperatinib administration at single doses up to 12 mg/kg when given orally to conscious telemetry-instrumented minipigs. At this dose, the C<sub>max</sub> corresponded to 909 ng/mL after a single dose which is approximately 0.3 times the human geometric mean maximum concentration (C<sub>max</sub> = 2980 ng/mL) at the clinical dose of 160 mg BID. In addition, there were no ECG changes after 28 days of repeated dosing in minipigs at doses up to 12 mg/kg which corresponded to a C<sub>max</sub> of 1120 ng/mL on Day 22. In contrast, female minipigs administered 5 mg/kg/day in the 91-day repeated-dose study were noted with a slight significant increase in QTc prolongation on Day 88 of the dosing phase. When comparing the percentage change in QTc on Day 88 for females administered 5 mg/kg/day with the time-matched percentage change in QTc

for the control group and pre-dose values, the prolongation in QTc for females was approximately 12% and 7 % increased, respectively. Based on the low magnitude of the QTc changes, these QTc changes were not considered adverse. The dose of 5 mg/kg/day corresponded to a mean Cmax of 565 ng/mL for females on Day 91 which is approximately 0.2 times the human geometric mean maximum concentration (Cmax = 2980 ng/mL) at the clinical dose of 160 mg BID.

## 3.2 SPONSOR'S RESULTS

### 3.2.1 By Time Analysis

Sponsor performed by-time point analysis using linear mixed model. Mean placebo-corrected  $\Delta$ QTcF peaked at 9.7 ms (90% CI: 6.98 to 12.47) at 2.5 hours postdose on the higher dose of LOXO-292 and at 8.1 ms (90% CI: 4.28 to 11.87) at 12 hours postdose on the lower dose. The largest upper bounds of 90% CI are 12.53 ms at 3 hours postdose on the higher dose and 11.87 ms at 12 hours postdose on the lower dose, respectively.

***Reviewer's comment:*** FDA reviewer performed by-time analysis using linear mixed model. FDA reviewer's by-time point analysis results are similar to the sponsor's results. As the original study was powered for exposure-response analysis not by-time analysis, the interpretation of this study should be based on exposure response analysis.

#### 3.2.1.1 Assay Sensitivity

The results of the sponsor's analysis shows that the study demonstrated assay sensitivity (lower bound at the geometric mean Cmax is > 5 msec).

***Reviewer's comment:*** The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.5.1 for additional details.

### 3.2.2 QT Bias Assessment

#### 3.2.2.1.1 QT Bias Assessment

Not applicable.

### 3.2.3 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., > 500 msec or > 60 msec over baseline, HR (<45 or >100 bpm), PR (>220 msec and 25% over baseline) and QRS (>120 msec and 25% over baseline).

***Reviewer's comment:*** FDA analysis results are similar to the sponsor's analysis.

### 3.2.4 Exposure-Response Analysis

The sponsor performed PK/PD analysis to explore the relationship between selpercatinib plasma concentration and  $\Delta$ QTcF (change from baseline in QTcF) using a linear mixed-effects approach.

The sponsor's model included  $\Delta$ QTcF as dependent variable, time-matched selpercatinib plasma concentration and centered baseline QTcF as continuous covariates, treatment and time as categorical factors, and a random intercept and slope per subject. The slope and

the treatment effect-specific intercept (defined as the difference between active and placebo) were estimated together with 2-sided 90% CI.

The results of the sponsor's analysis shows an absence of significant QTc prolongation up to 2356 ng/mL, which was C<sub>max</sub> observed following the highest dose evaluated.

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

### **3.2.5 Cardiac Safety Analysis**

There were no deaths, SAEs, or subject discontinuations due to AEs. The only cardiac related AE was in one subject who experienced palpitations in the 320 mg LOXO-292 group.

Subject (b) (6) (a 36-year-old White male; Treatment Sequence ABCD) experienced the Grade 1 TEAE of palpitations (verbatim term: heart skipped a beat). The event occurred approximately 14 hours after dosing with 320 mg LOXO-292 and resolved within 1 minute. During a routine AE assessment on Day 2 of Period 1, the subject reported to clinic staff of having experienced the sensation that his heart skipped a beat during the night prior to the assessment which resolved spontaneously. He denied shortness of breath, pain or discomfort to the chest, or numbness to arms. No instances of arrhythmia or palpitations were observed in the Holter monitor data at the time of the AE, and no safety ECGs or vital signs were obtained at that time.

***Reviewer's comment:*** *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., 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, which is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 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**

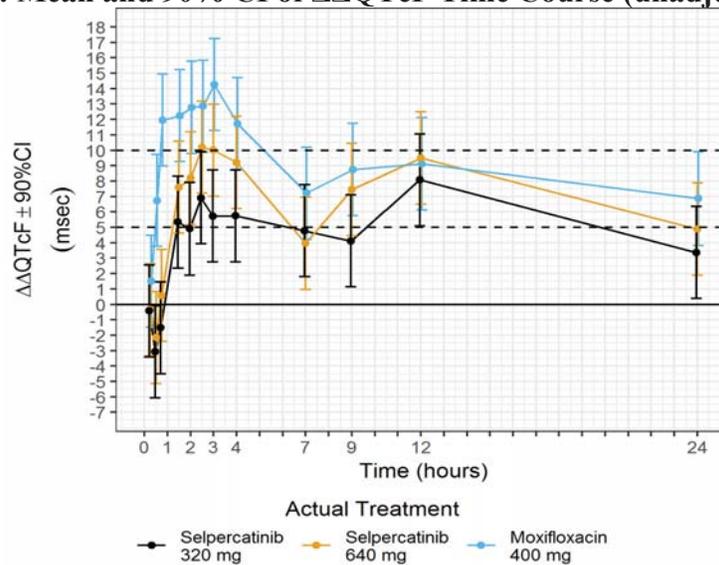
The analysis population used for by time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used linear mixed model to analyze the drug effect by time for each biomarker (e.g.,  $\Delta\text{QTcF}$ ,  $\Delta\text{HR}$ ) 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 association between repeated measures within period.

### 4.3.1 QTc

Figure 1 displays the time profile of  $\Delta\Delta\text{QTc}$  for different treatment groups. The maximum  $\Delta\Delta\text{QTc}$  values by treatment are shown in Table 2.

**Figure 1: Mean and 90% CI of  $\Delta\Delta\text{QTcF}$  Time Course (unadjusted CIs).**



**Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for  $\Delta\Delta\text{QTc}$**

Actual Treatment	Time (hours)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)
Selpercatinib 320 mg	12.0	8.1	(5.1 to 11.1)
Selpercatinib 640 mg	2.5	10.2	(7.2 to 13.2)

#### 4.3.1.1 Assay sensitivity

FDA reviewer used the same model for assay sensitivity. The time-course of changes in  $\Delta\Delta\text{QTc}$  is shown in Figure 1 and shows the expected time-profile with a mean effect of  $> 5$  msec after Bonferroni adjustment for 4 time points (Table 3).

**Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for  $\Delta\Delta\text{QTc}$**

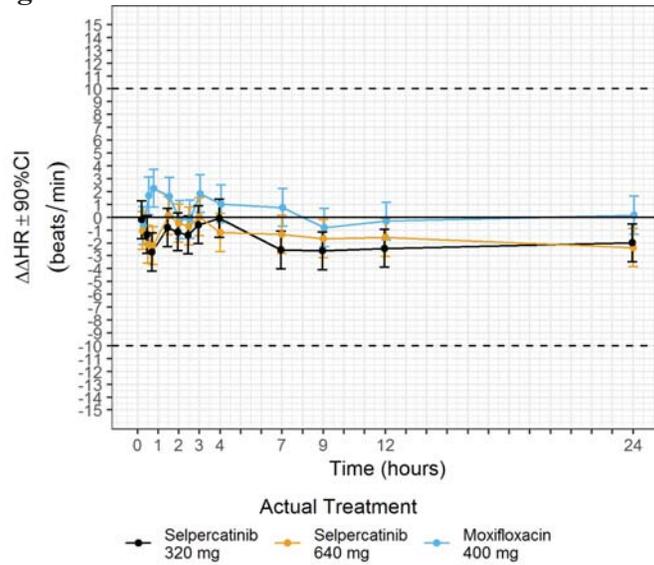
Actual Treatment	Time (hours)	$\Delta\Delta\text{QTcF}$ (msec)	90% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	3.0	14.3	(11.3 to 17.2)	(10.2 to 18.3)

The primary method for establishing assay sensitivity for this study was based on exposure response analysis - see section 4.5.1.1 for details.

### 4.3.2 HR

Figure 2 displays the time profile of  $\Delta\Delta\text{HR}$  for different treatment groups.

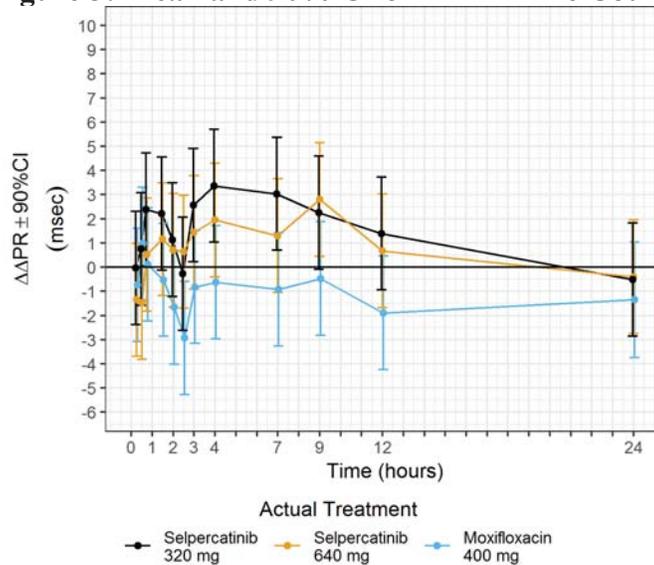
**Figure 2: Mean and 90% CI of  $\Delta\Delta\text{HR}$  Time Course**



### 4.3.3 PR

Figure 3 displays the time profile of  $\Delta\Delta\text{PR}$  for different treatment groups.

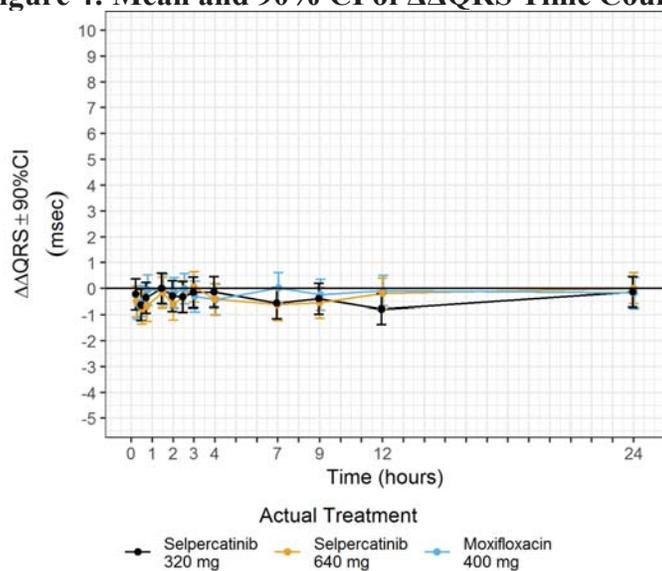
**Figure 3: Mean and 90% CI of  $\Delta\Delta\text{PR}$  Time Course**



### 4.3.4 QRS

Figure 4 displays the time profile of  $\Delta\Delta\text{QRS}$  for different treatment groups.

**Figure 4: Mean and 90% CI of  $\Delta\Delta$ QRS 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

None of the subjects experienced QTcF and  $\Delta$ QTcF greater than 480 msec and greater than 60 ms respectively.

##### 4.4.2 HR

None of the subjects experienced HR greater than 100 bpm or less than 45 bpm in any of the dose levels of selpercatinib.

##### 4.4.3 PR

None of the subjects experienced PR greater than 220 msec in any of the dose levels of selpercatinib.

##### 4.4.4 QRS

None of the subjects experienced QRS greater than 120 msec in any of the dose levels of selpercatinib.

#### 4.5 EXPOSURE-RESPONSE ANALYSIS

All randomized subjects (n=32) were included in the exposure-response analysis. Subject <sup>(b) (6)</sup> was excluded from the calculation of C<sub>max</sub> of selpercatinib (640 mg) dose group due to receiving 7 out of 8 capsules (80 mg per capsule) but was included in the assay sensitivity analysis and in the concentration-QTc analysis.

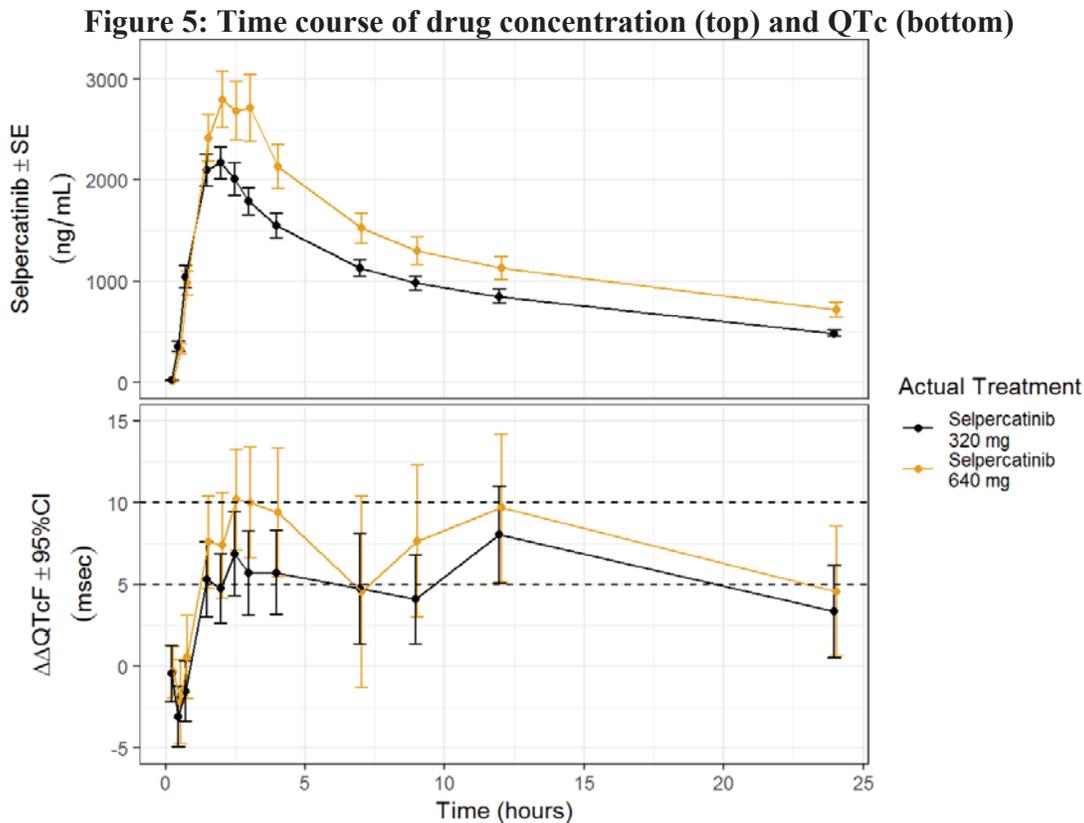
### 4.5.1 QTc

Prior to evaluating the relationship 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  $\Delta$ QTc and 3) presence of non-linear relationship.

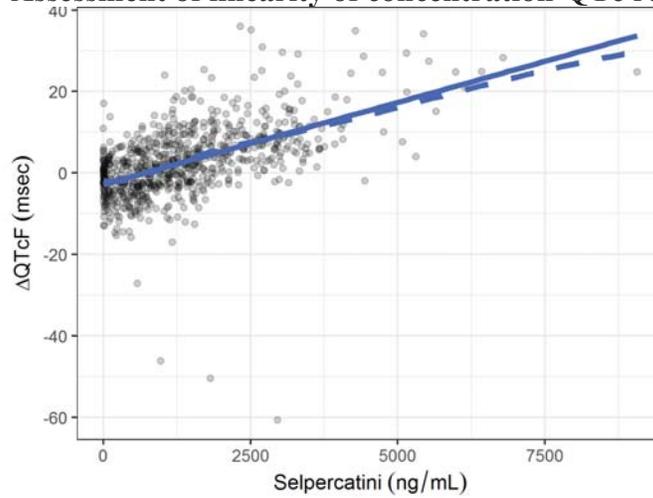
Figure 2 shows the time-course of  $\Delta\Delta$ HR, which shows an absence of significant  $\Delta\Delta$ HR changes.

Figure 5 evaluates the time-course of selpercatinib-concentration and  $\Delta\Delta$ QTc. A delay of 10 hours between Cmax and the largest QT effect was observed for the 320 mg dose. Similarly, a substantial QT effect was observed at the 12 hour time point for the 640 mg dose, though the largest QT effect was observed near Tmax. The large  $\Delta\Delta$ QTcF at 12 hour time point was thought to be driven by the reduction in the  $\Delta$ QTcF in the placebo cohort (-5.8 ms), while the  $\Delta$ QTcF values were 2.2 msec and 3.0 msec for 320 mg dose and 640 mg dose, respectively (Table 14.2.3.1.3.1 (p.g.154), CSR #CA25494). Therefore, this analysis does not suggest the presence of significant PK/PD hysteresis.

Figure 6 shows the relationship between selpercatinib concentration and  $\Delta$ QTc and supports the use of a linear model.

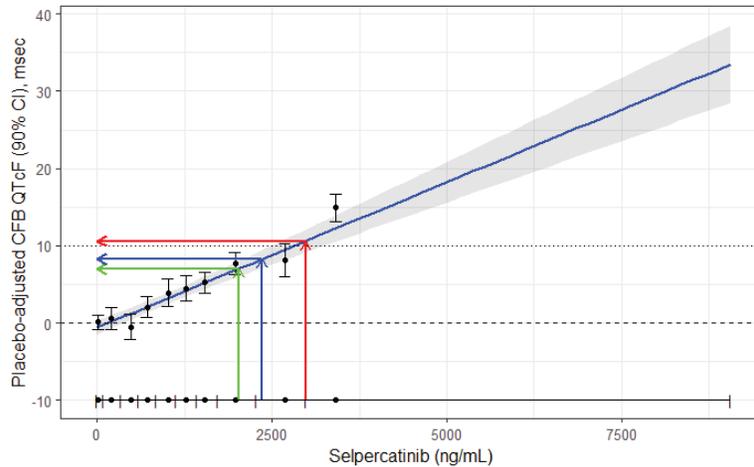


**Figure 6: Assessment of linearity of concentration-QTc relationship**



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

**Figure 7: Goodness-of-fit plot for QTc.** Green: 320 mg; Blue: 640 mg; Red: the proposed therapeutic dose (160 mg BID)



**Table 4: Predictions from concentration-QTc model**

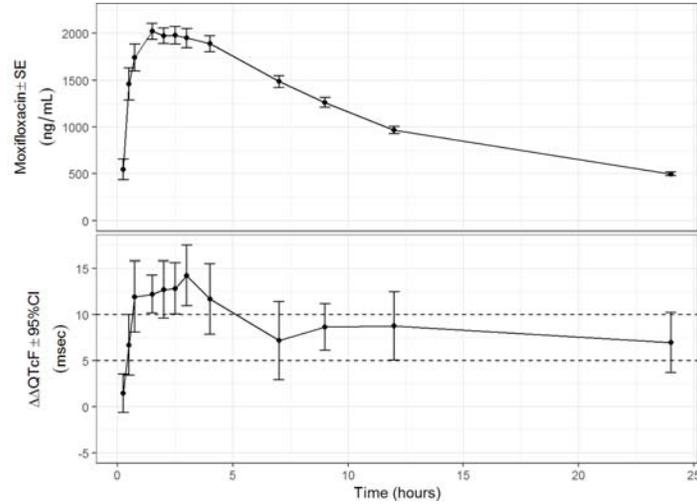
Actual Treatment	Selpercatinib (ng/mL)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)
Selpercatinib 320 mg	2,024.5	7.0	(6.0 to 8.0)
Selpercatinib 640 mg	2,355.5	8.3	(7.1 to 9.4)
Therapeutic concentration	2,980.0	10.6	(9.1 to 12.1)

#### 4.5.1.1 Assay sensitivity

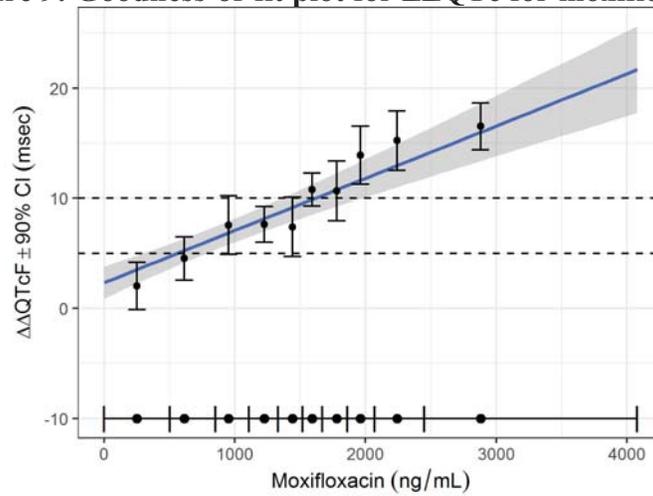
To demonstrate assay sensitivity, the sponsor included oral moxifloxacin 400 mg as a positive control to detect small increases from baseline for QTcF in this study. The PK profile in the moxifloxacin group are generally consistent with the ascending, peak, and descending phases of historical data (Figure 8). Concentration-response analysis of moxifloxacin data indicated a positive slope in the relationship between  $\Delta\text{QTcF}$  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 ms. The goodness-of-fit plot for moxifloxacin is shown in Figure 9 and the predicted QTc at the geometric mean C<sub>max</sub> is listed in Table 5.

**Figure 8. Time course of moxifloxacin concentration and QTcF**



**Figure 9: Goodness-of-fit plot for ΔΔQTcF for moxifloxacin**



**Table 5: Predictions from concentration-QTc model for moxifloxacin**

Actual Treatment	Moxifloxacin (ng/mL)	ΔΔQTcF (msec)	90.0% CI (msec)
Moxifloxacin 400 mg	2,309	13.3	(11.3 to 15.3)

-----  
**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  
03/04/2020 11:39:09 AM  
Jihye Ahn is the primary clinical pharmacology reviewer.

JIHYE AHN  
03/04/2020 11:55:32 AM

FERDOUSE BEGUM  
03/04/2020 12:33:01 PM

DALONG HUANG  
03/04/2020 12:34:19 PM

MICHAEL Y LI  
03/04/2020 12:47:07 PM

LARS JOHANNESSEN  
03/04/2020 01:47:57 PM

CHRISTINE E GARNETT  
03/06/2020 02:07:27 PM

## Clinical Inspection Summary

<b>Date</b>	02/27/2020
<b>From</b>	Michele Fedowitz, MD, Medical Officer Yang-Min (Max) Ning, MD, PhD., Acting Team Leader Kassa Ayalew, MD, MPH, Branch Chief Good Clinical Practice Assessment Branch(GCPAB) Division of Clinical Compliance Evaluation(DCCE) Office of Scientific Investigations (OSI)
<b>To</b>	Suzanne Demko, P.A.-C., Cross Discipline Team Lead Diana Bradford, M.D., Clinical Reviewer Harpreet Singh, M.D., Acting Division Director Autumn Zack-Taylor, Regulatory Project Manager Division of Oncology 2 (DO2)
<b>NDA #</b>	213246
<b>Applicant</b>	Loxo Oncology, Inc
<b>Drug</b>	RETEVMO (selpercatinib), also known as LOXO-292
<b>NME (Yes/No)</b>	YES
<b>Therapeutic Classification</b>	Tyrosine kinase inhibitor
<b>Proposed Indication(s)</b>	<ul style="list-style-type: none"> <li>For the treatment of patients with RET-mutant medullary thyroid cancer (MTC) who require systemic therapy, have progressed following prior treatment and have no acceptable alternative treatment options; and for the treatment of patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) who required systemic therapy and have progressed following platinum-based chemotherapy and anti-PD-1 or anti-PD-L1 therapy</li> </ul>
<b>Consultation Request Date</b>	12/17/2019
<b>Summary Goal Date</b>	03/02/2020
<b>Action Goal Date</b>	05/01/2020
<b>PDUFA Date</b>	08/04/2020

### I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical data from an ongoing Phase 1/2 trial (Study LOXO-RET-17001) was submitted to the Agency in support of a New Drug Application (NDA 213246) for RETEVMO (selpercatinib) in adult (b) (4) patients with metastatic rearranged during transfection (RET) fusion positive non-small cell lung cancer (NSCLC) and RET-mutant medullary thyroid cancer (MTC). Three clinical investigators, Manisha Shah (Site 105), Vivek Subbiah (Site

103), and Lori Wirth (Site 109) were selected for inspections.

The on-site inspections of the three audited clinical investigator sites revealed no significant findings related to the data integrity or human subject protection in the study LOXO-RET-17001. There was no evidence of underreporting of adverse events. Based on the inspections, the data generated by the inspected clinical sites, submitted by the Applicant, appear to be acceptable in support of the NDA.

## II. BACKGROUND

Loxo Oncology, Inc. seeks accelerated approval of RETEVMO (selpercatinib) for the treatment of patients with *RET* fusion-positive NSCLC or *RET*-mutant medullary thyroid cancer (MTC). To support the proposed indications, the Applicant submitted data from Study LOXO-RET-17001(NCT03157128), an on-going, multicenter, open-label, Phase 1/2 study in patients with advanced solid tumors, including *RET* fusion-positive solid tumors, *RET*-mutant MTC, and other tumors with *RET* activation.

The study includes two parts: Phase 1 (dose escalation) and Phase 2 (dose expansion). The Phase 1 part was to determine a Recommended Phase 2 Dose (RP2D) of selpercatinib for the study. The Phase 2 part of this study was to characterize the safety and efficacy of selpercatinib in subjects with specific abnormalities in *RET*. Subjects eligible for the Phase 2 were required to have evidence of a *RET* gene alteration in tumor and were planned to be enrolled into one of the following 5 cohorts based on tumor type, *RET* alteration, and prior treatment. Subjects received study treatment at the RP2D orally twice daily (BID) until unacceptable toxicity or disease progression.

Cohort 1: subjects with *RET* fusion-positive solid tumors who had received standard therapy

Cohort 2: subjects with *RET* fusion-positive solid tumors without prior standard therapy

Cohort 3: subjects with *RET*-mutant MTC who had received standard cabozantinib and/or vandetanib

Cohort 4: subjects with *RET*-mutant MTC without prior standard cabozantinib and/or vandetanib or other kinase inhibitor

Cohort 5: subjects who had an advanced *RET*-altered solid tumor who did not otherwise qualify for Cohorts 1 through 4

The primary endpoint for the Phase 2 portion was to evaluate the objective response rate (ORR) by imaging (RECIST 1.1 or RANO, as appropriate to the tumor type) as assessed by an independent review committee.

From May 9, 2017 through June 17, 2019 (the data cutoff date for the interim analysis), this study enrolled 531 subjects from 84 investigational sites in Australia, Canada, Denmark, Germany, Japan, Hong Kong, Israel, Singapore, France, Italy, Spain, South Korea, Switzerland, Taiwan, and the U.S. Sixty-five percent of subjects were recruited from the U.S.

Of the enrolled subjects, the majority of subjects (n = 439) started selpercatinib at the RP2D of 160 mg BID. At the time of this interim analysis, 304 (57.3%) subjects were eligible for

response analysis. Response evaluable (“eligible”) subjects were those in the analysis set who had an opportunity to be followed for at least 6 months from the first dose of selpercatinib to the data cutoff date. The 304 evaluable subjects included 109 in Cohort 1, 17 in Cohort 2, 77 in Cohort 3, 34 in Cohort 4, and 67 in Cohort 5.

The Review Division and OSI selected three clinical investigators (CI), Drs. Manisha Shah (Site 105), Vivek Subbiah (Site 103), and Lori Wirth (Site 109) for inspection. The three sites had relatively high enrollments and high treatment responders. In addition, Dr. Shah had regulatory violations noted in three prior FDA inspections conducted in 2005, 2012, and 2014. The reported observations included “Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation” and “Investigation not conducted in accordance with the investigational plan”.

*Reviewer’s Comments: All treated subjects were included in the safety analysis. Subjects treated during the Phase 1 portion of the study who met the Phase 2 eligibility criteria for one of the Phase 2 cohorts were included as part of the evaluable patients for that cohort for the efficacy analyses. The clinical inspections included a review of all subjects from all cohorts at each selected site, including subjects with NSCLC (in Cohorts 1 and 2) and MTC (in Cohorts 3 and 4) for the proposed indication.*

### III. RESULTS

#### 1. Vivek Subbiah, Clinical Investigator Site 103

1515 Holcombe Blvd, Unit 455  
Houston, TX 77030

This CI was inspected between January 8 and January 14, 2020 as a data audit for the study LOXO-RET-17001. This was the first FDA inspection for this investigator. This site enrolled subjects for both Phase 1 and Phase 2 portions and the first patient was dosed on 6/21/2017. At the time of data cutoff of 07/04/2019, 58 subjects were screened, 53 were enrolled at the site, with 10 subjects in Phase 1 and 43 subjects in Phase 2. Eight (8) subjects had discontinued the study, including 6 deaths (Subjects (b) (6)) and 2 subjects withdrew consent (Subjects (b) (6)).

The inspection included a review of documents related to the site’s IRB approval and correspondences, site training, site monitoring, investigational product accountability, and financial disclosures. A comprehensive review of the source document records regarding screening and enrollment, concomitant medications, informed consent, adverse events, and primary endpoint data was performed for 45 enrolled subjects.

The data listings submitted in the NDA were reviewed and verified by comparison with source data at the site. The primary endpoint data was verifiable and there was no evidence of under-reporting of adverse events (AEs) or protocol violations.

The inspection revealed no significant deficiencies, with no Form FDA 483 issued to the investigator.

**2. Manisha Shah, Clinical Investigator Site 105**

2050 Kenny Road  
Columbus, OH 43221

This CI was inspected between January 27, 2020 and February 7, 2020 as a data audit for the study LOXO-RET-17001. This was the fourth inspection of this investigator. The three prior inspections, as mentioned in the above section of this summary, identified regulatory deficiencies. Each of the inspections had a compliance classification of Voluntary Action Indication.

This site enrolled subjects for both Phase 1 and Phase 2 portions. A total of 34 subjects were screened at the site, with 30 subjects enrolled. Nine subjects were allocated to Phase 1 and 21 to Phase 2. As of the data cutoff date, 3 patients died (Subjects [REDACTED]<sup>(b) (6)</sup>) and one subject (Subject [REDACTED]<sup>(b) (6)</sup>) had early discontinuation due to adverse events.

A comprehensive review of the source documents regarding the informed consent, eligibility and endpoint data was performed for all 30 enrolled subjects. All source records were in good condition, organized, and legible. The data listings submitted in the NDA were verifiable with the reviewed source data at the site.

A two-item Form FDA 483 was issued at the end of the inspection, stating that the investigation was not conducted in accordance with the investigational plan. Specifically, the following protocol-required assessments were not completed:

1. There were 8 thyroid function tests on 5 subjects (Subjects [REDACTED]<sup>(b) (6)</sup>) that were not performed at the required timepoints; and 4 of these thyroid function tests on 2 subjects (Subjects [REDACTED]<sup>(b) (6)</sup>) were not reported as protocol deviations
2. Nine (9) EORTC QLQ-C30 or PedsQL were not performed at the required timepoints for 5 subjects (Subjects [REDACTED]<sup>(b) (6)</sup>) according to protocol; and were not reported as protocol deviations

*Reviewer's Comments: Given the inspection completion date, OSI has not received a written response to the listed Observations from Dr. Shah. Based on information contained in the clinical study report and the proposed label, these two Observations do not appear to affect the primary endpoint.*

**3. Lori Wirth, Site 109**

55 Fruit Street  
Boston, MA 02114

This CI was inspected between January 30 and February 10, 2020 as a data audit for the study LOXO-RET-17001. This was the first FDA inspection for this investigator. This site enrolled both phase 1 and phase 2 patients. Currently, the established inspection report is not available. Based on the preliminary inspection summary, the site screened a total of 35 subjects and enrolled 34. At the time of inspection, 25 subjects were in active

treatment and nine subjects were off study treatment, including 5 deaths (Subjects (b) (6) [redacted]), 3 in follow-up phase (Subjects (b) (6) [redacted]), and one withdrawal (Subject (b) (6) [redacted]).

The inspection included a review of documents related to the site's IRB approval and correspondences, site monitoring, investigational product accountability, and financial disclosures, consent, and general protocol compliance.

A comprehensive review of the source document records for all 34 enrolled subjects was performed, including adverse events and primary endpoint data. The data listings submitted in the NDA were compared with source data at the site. The primary endpoint data was verifiable and there was no evidence of under-reporting of AEs.

The inspection reported no significant deficiencies, with no Form FDA 483 issued to the investigator.

Note that an amendment to this inspection summary will be introduced if the EIR for Dr. Lori Wirth contains considerable differences that can change the current GCP assessment and compliance conclusion for this CI site.

Michele Fedowitz, M.D.  
Good Clinical Practice Enforcement *or* Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

Yang-Min (Max) Ning, MD, PhD., M.D.,  
Acting Team Leader,  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

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  
02/27/2020 01:36:28 PM

YANGMIN NING  
02/27/2020 01:43:21 PM

KASSA AYALEW  
03/02/2020 09:51:44 AM