CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

213246Orig1s008

Trade Name:	**RETEVMO**
Generic or Proper Name:	(selpercatinib)
Sponsor:	ELI LILLY AND CO
Approval Date:	September 21, 2022

Indication:

RETEVMO is a kinase inhibitor indicated for the treatment of:

- Adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a rearranged during transfection (RET) gene fusion, as detected by an FDA- approved test
- Adult and pediatric patients 12 years of age and older with advanced or metastatic medullary thyroid cancer (MTC) with a RET mutation, as detected by an FDA- approved test, who require systemic therapy
- Adult and pediatric patients 12 years of age and older with advances or metastatic thyroid cancer with RET gene fusion, as detected by an FDA- approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)
- Adult patients with locally advanced or metastatic solid tumors with a RET gene fusion, as detected by an FDA- approved test, that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 212346/S-008

ACCELERATED APPROVAL

Loxo Oncology Inc., a wholly owned subsidiary of Eli Lilly and Company
Attention: Viktoriya Ilaria
Sr. Director—Global Regulatory Affairs—North America
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Ilaria:

Please refer to your supplemental new drug application (sNDA) dated and received May 31, 2022, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for RETEVMO (selpercatinib) capsules.

This "Prior Approval" sNDA provides for use of RETEVMO (selpercatinib) capsules, for oral use for adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated September 13, 2022. This requirement, along with required completion dates, is listed below.

4342-1 Complete clinical trial(s) to obtain data on the clinical efficacy of selpercatinib through more precise estimation of the overall response rate and mature response duration per independent review assessment, in at least 60 patients with locally advanced or metastatic *RET*-fusion positive solid tumors other than non-small cell lung cancer and thyroid cancer, who have progressed on prior systemic treatment or have no satisfactory

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

alternative treatment options. A sufficient number of patients with tumor types for which responses require additional characterization (e.g., colorectal cancer, esophagogastric cancer, and glioma) will be evaluated. Overall response rate and duration of response will be assessed by independent central review and all responding patients will be followed for at least 12 months following the onset of response or until disease progression or death or early treatment discontinuation, whichever comes first. Include available data regarding *RET* fusion partners and co-occurring genetic alterations for all patients.

Trial Completion: 06/2025
Final Report Submission: 12/2025

Submit clinical protocols to your IND 133193 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this post marketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4342-2 Commitment to support the availability of an in vitro diagnostic device that demonstrates the device is essential to the safe and effective use of selpercatinib for treatment of patients with *RET* fusion-positive solid

tumors through an appropriate analytical and clinical validation study using clinical trial data.

The timetable you submitted on September 13, 2022, states that you will conduct this study according to the following schedule:

Study Completion:	09/2023
Final Report Submission:	03/2024

Submit clinical protocols to your IND 133193 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials)

at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[3]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Maritsa Stephenson, Regulatory Health Project Manager, at 301-796-1760.

Sincerely,

{See appended electronic signature page}

Harpreet Singh, M.D.
Director
Division of Oncology 2
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

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/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213246Orig1s008

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RETEVMO safely and effectively. See full prescribing information for RETEVMO.

RETEVMO® (selpercatinib) capsules, for oral use

Initial U.S. Approval: 2020

RECENT MAJOR CHANGES

Indications and Usage (1.1, 1.2, 1.3,1.4)	09/2022
Dosage and Administration, Patient Selection (2.1, 2.5)	09/2022
Warnings and Precautions (5.2, 5.9)	09/2022

INDICATIONS AND USAGE

RETEVMO® is a kinase inhibitor indicated for the treatment of:

- Adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a *rearranged during transfection (RET)* gene fusion, as detected by an FDA-approved test (1.1)
- Adult and pediatric patients 12 years of age and older with advanced or metastatic medullary thyroid cancer (MTC) with a *RET* mutation, as detected by an FDA-approved test, who require systemic therapy[1] (1.2)
- Adult and pediatric patients 12 years of age and older with advanced or metastatic thyroid cancer with a *RET* gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)[1] (1.3)
- Adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options[1] (1.4)

[1] This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

DOSAGE AND ADMINISTRATION

- Select patients for treatment with RETEVMO based on the presence of a *RET* gene fusion (NSCLC, thyroid, or other solid tumors) or specific *RET* gene mutation (MTC). (2.1, 14)
- Recommended dosage in adults and pediatric patients 12 years of age or older is based on weight (2.3):
  - Less than 50 kg: 120 mg orally twice daily
  - 50 kg or greater: 160 mg orally twice daily
- Reduce RETEVMO dose in patients with severe hepatic impairment. (2.7, 8.7)

DOSAGE FORMS AND STRENGTHS

- Capsules: 40 mg, 80 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- *Hepatotoxicity:* Monitor ALT and AST prior to initiating RETEVMO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose, or permanently discontinue RETEVMO based on severity. (2.5, 5.1)
- *Interstitial Lung Disease (ILD)/Pneumonitis*: Monitor for new or worsening pulmonary symptoms. Withhold, reduce the dose or permanently discontinue RETEVMO based on severity. (2.5, 5.2)
- *Hypertension:* Do not initiate RETEVMO in patients with uncontrolled hypertension. Optimize blood pressure (BP) prior to initiating RETEVMO. Monitor BP after 1 week, at least monthly thereafter and as clinically indicated. Withhold, reduce dose, or permanently discontinue RETEVMO based on severity. (2.5, 5.3)
- *QT Interval Prolongation:* Monitor patients who are at significant risk of developing QTc prolongation. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment. Monitor QT interval more frequently when RETEVMO is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue RETEVMO based on severity. (2.5, 5.4)
- *Hemorrhagic Events:* Permanently discontinue RETEVMO in patients with severe or life-threatening hemorrhage. (2.5, 5.5)
- *Hypersensitivity:* Withhold RETEVMO and initiate corticosteroids. Upon resolution, resume at a reduced dose and increase dose by 1 dose level each week until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. (2.5, 5.6)
- *Tumor Lysis Syndrome:* Closely monitor patients at risk and treat as clinically indicated. (5.7)
- *Risk of Impaired Wound Healing:* Withhold RETEVMO for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of RETEVMO after resolution of wound healing complications has not been established. (5.8)
- *Hypothyroidism:* Monitor thyroid function before treatment with RETEVMO and periodically during treatment. Withhold until clinically stable or permanently discontinue based on severity. (5.9)
- *Embryo-Fetal Toxicity:* Can cause fetal harm. Advise females of reproductive potential of the possible risk to a fetus and to use effective contraception. (5.10, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (≥25%) were edema, diarrhea, fatigue, dry mouth, hypertension, abdominal pain, constipation, rash, nausea, and headache. (6)

The most common Grade 3 or 4 laboratory abnormalities (≥5%) were decreased lymphocytes, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), decreased sodium, and decreased calcium. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- *Acid-Reducing Agents:* Avoid coadministration. If coadministration cannot be avoided, take RETEVMO with food (with PPI) or modify its administration time (with H2 receptor antagonist or locally-acting antacid). (2.4, 7.1)
- *Strong and Moderate CYP3A Inhibitors:* Avoid coadministration. If coadministration cannot be avoided, reduce the RETEVMO dose. (2.6, 7.1)
- *Strong and Moderate CYP3A Inducers:* Avoid coadministration. (7.1)
- *CYP2C8 and CYP3A Substrates:* Avoid coadministration. If coadministration cannot be avoided, modify the substrate dosage as recommended in its product labeling. (7.2)
- *Certain P-gp Substrates:* Avoid coadministration. If coadministration cannot be avoided, modify the substrate dosage as recommended in its product labeling. (7.2)

USE IN SPECIFIC POPULATIONS

- *Lactation: Advise not to breastfeed.* (8.2)
- *Pediatric Use:* Monitor open growth plates in adolescent patients. Consider interrupting or discontinuing RETEVMO if abnormalities occur. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 *RET* Fusion-Positive Non-Small Cell Lung Cancer

RETEVMO® is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a *rearranged during transfection (RET)* gene fusion, as detected by an FDA-approved test.

1.2 *RET*-Mutant Medullary Thyroid Cancer

RETEVMO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic medullary thyroid cancer (MTC) with a *RET* mutation, as detected by an FDA-approved test, who require systemic therapy.

This indication is approved under accelerated approval based on overall response rate and duration of response *[see Clinical Studies (14.2)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

1.3 *RET* Fusion-Positive Thyroid Cancer

RETEVMO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic thyroid cancer with a *RET* gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

This indication is approved under accelerated approval based on overall response rate and duration of response *[see Clinical Studies (14.3)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

1.4 Other *RET* Fusion-Positive Solid Tumors

RETEVMO is indicated for the treatment of adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.

This indication is approved under accelerated approval based on overall response rate and duration of response *[see Clinical Studies (14.4)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for treatment with RETEVMO based on the presence of a *RET* gene fusion (NSCLC, thyroid cancer, or other solid tumors) or specific *RET* gene mutation (MTC) in tumor specimens *[see Clinical Studies (14)]*. Information on FDA-approved test(s) for the detection of *RET* gene fusions and *RET* gene mutations is available at: http://www.fda.gov/CompanionDiagnostics. An FDA-approved companion diagnostic test for the detection of *RET* gene fusions and *RET* gene mutations in plasma or in tumors other than NSCLC and thyroid cancer is not currently available.

2.2 Important Administration Instructions

RETEVMO may be taken with or without food unless coadministered with a proton pump inhibitor (PPI) *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

2.3 Recommended Dosage

The recommended dosage of RETEVMO based on body weight is:

- Less than 50 kg: 120 mg
- 50 kg or greater: 160 mg

Take RETEVMO orally twice daily (approximately every 12 hours) until disease progression or unacceptable toxicity.

Swallow the capsules whole. Do not crush or chew the capsules.

Do not take a missed dose unless it is more than 6 hours until next scheduled dose.

If vomiting occurs after RETEVMO administration, do not take an additional dose and continue to the next scheduled time for the next dose.

2.4 Dosage Modifications for Concomitant Use of Acid-Reducing Agents

Avoid concomitant use of a PPI, a histamine-2 (H2) receptor antagonist, or a locally-acting antacid with RETEVMO *[see Drug Interactions (7.1)]*. If concomitant use cannot be avoided:

- Take RETEVMO with food when coadministered with a PPI.
- Take RETEVMO 2 hours before or 10 hours after administration of an H2 receptor antagonist.
- Take RETEVMO 2 hours before or 2 hours after administration of a locally-acting antacid.

2.5 Dosage Modifications for Adverse Reactions

The recommended dose reductions for adverse reactions are provided in Table 1.

Table 1: Recommended RETEVMO Dose Reductions for Adverse Reactions

Dose Reduction	Patients Weighing Less Than 50 kg	Patients Weighing 50 kg or Greater
First	80 mg orally twice daily	120 mg orally twice daily
Second	40 mg orally twice daily	80 mg orally twice daily
Third	40 mg orally once daily	40 mg orally twice daily

Permanently discontinue RETEVMO in patients unable to tolerate three dose reductions.

The recommended dosage modifications for adverse reactions are provided in Table 2.

Table 2: Recommended RETEVMO Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Hepatotoxicity *[see Warnings and Precautions (5.1)]*	Grade 3 or Grade 4	• Withhold RETEVMO and monitor AST/ALT once weekly until resolution to Grade 1 or baseline. • Resume at reduced dose by 2 dose levels and monitor AST and ALT once weekly until 4 weeks after reaching dose taken prior to the onset of Grade 3 or 4 increased AST or ALT. • Increase dose by 1 dose level after a minimum of 2 weeks without recurrence and then increase to dose taken prior to the onset of Grade 3 or 4 increased AST or ALT after a minimum of 4 weeks without recurrence.
Interstitial Lung Disease/ Pneumonitis *[see Warnings and Precautions (5.2)]*	Grade 2	• Withhold RETEVMO until resolution. • Resume at a reduced dose. • Discontinue RETEVMO for recurrent ILD/pneumonitis.
	Grade 3 or Grade 4	• Discontinue RETEVMO for confirmed ILD/pneumonitis.
Hypertension *[see Warnings and Precautions (5.3)]*	Grade 3	• Withhold RETEVMO for Grade 3 hypertension that persists despite optimal antihypertensive therapy. Resume at a reduced dose when hypertension is controlled.
	Grade 4	• Discontinue RETEVMO.
QT Interval Prolongation *[see Warnings and Precautions (5.4)]*	Grade 3	• Withhold RETEVMO until recovery to baseline or Grade 0 or 1. • Resume at a reduced dose.
	Grade 4	• Discontinue RETEVMO.
Hemorrhagic Events *[see Warnings and Precautions (5.5)]*	Grade 3 or Grade 4	• Withhold RETEVMO until recovery to baseline or Grade 0 or 1. • Discontinue RETEVMO for severe or life-threatening hemorrhagic events.
Hypersensitivity Reactions *[see Warnings and Precautions (5.6)]*	All Grades	• Withhold RETEVMO until resolution of the event. Initiate corticosteroids. • Resume at a reduced dose by 3 dose levels while continuing corticosteroids. • Increase dose by 1 dose level each week until the dose taken prior to the onset of hypersensitivity is reached, then taper corticosteroids.
Hypothyroidism *[see Warnings and Precautions (5.9)]*	Grade 3 or Grade 4	• Withhold RETEVMO until resolution to Grade 1 or baseline. • Discontinue RETEVMO based on severity.
Other Adverse Reactions *[see Adverse Reactions (6.1)]*	Grade 3 or Grade 4	• Withhold RETEVMO until recovery to baseline or Grade 0 or 1. • Resume at a reduced dose.

2.6 Dosage Modifications for Concomitant Use of Strong and Moderate CYP3A Inhibitors

Avoid concomitant use of strong and moderate CYP3A inhibitors with RETEVMO. If concomitant use of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the RETEVMO dose as recommended in Table 3. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume RETEVMO at the dose taken prior to initiating the CYP3A inhibitor *[see Drug Interactions (7.1)]*.

Table 3: Recommended RETEVMO Dosage for Concomitant Use of Strong and Moderate CYP3A Inhibitors

Current RETEVMO Dosage	Recommended RETEVMO Dosage	
	Moderate CYP3A Inhibitor	Strong CYP3A Inhibitor
120 mg orally twice daily	80 mg orally twice daily	40 mg orally twice daily
160 mg orally twice daily	120 mg orally twice daily	80 mg orally twice daily

2.7 Dosage Modification for Severe Hepatic Impairment

Reduce the recommended dosage of RETEVMO for patients with severe hepatic impairment as recommended in Table 4 *[see Use in Specific Populations (8.7)]*.

Table 4: Recommended RETEVMO Dosage for Severe Hepatic Impairment

Current RETEVMO Dosage	Recommended RETEVMO Dosage
120 mg orally twice daily	80 mg orally twice daily
160 mg orally twice daily	80 mg orally twice daily

3 DOSAGE FORMS AND STRENGTHS

Capsules:

- 40 mg: gray opaque capsule imprinted with “Lilly”, “3977” and “40 mg” in black ink.
- 80 mg: blue opaque capsule imprinted with “Lilly”, “2980” and “80 mg” in black ink.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Serious hepatic adverse reactions occurred in 3% of patients treated with RETEVMO. Increased AST occurred in 59% of patients, including Grade 3 or 4 events in 11% and increased ALT occurred in 55% of patients, including Grade 3 or 4 events in 12% *[see Adverse Reactions (6.1)]*. The median time to first onset for increased AST was 6 weeks (range: 1 day to 3.4 years) and increased ALT was 5.8 weeks (range: 1 day to 2.5 years).

Monitor ALT and AST prior to initiating RETEVMO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue RETEVMO based on the severity *[see Dosage and Administration (2.5)]*.

5.2 Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, and fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with RETEVMO. ILD/pneumonitis occurred in 1.8% of patients who received RETEVMO, including 0.3% with Grade 3 or 4 events, and 0.3% with fatal reactions.

Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Withhold RETEVMO and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue RETEVMO based on severity of confirmed ILD [*see Dosage and Administration (2.5)*].

5.3 Hypertension

Hypertension occurred in 41% of patients, including Grade 3 hypertension in 20% and Grade 4 in one (0.1%) patient *[see Adverse Reactions (6.1)]*. Overall, 6.3% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications.

Do not initiate RETEVMO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating RETEVMO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue RETEVMO based on the severity *[see Dosage and Administration (2.5)]*.

5.4 QT Interval Prolongation

RETEVMO can cause concentration-dependent QT interval prolongation *[see Clinical Pharmacology (12.2)]*. An increase in QTcF interval to >500 ms was measured in 7% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 20% of patients *[see Adverse Reactions (6.1)]*. RETEVMO has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction.

Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating RETEVMO and during treatment.

Monitor the QT interval more frequently when RETEVMO is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue RETEVMO based on the severity *[see Dosage and Administration (2.5)]*.

5.5 Hemorrhagic Events

Serious including fatal hemorrhagic events can occur with RETEVMO. Grade ≥3 hemorrhagic events occurred in 3.1% of patients treated with RETEVMO, including 4 (0.5%) patients with fatal hemorrhagic events, including cerebral hemorrhage (n = 2), tracheostomy site hemorrhage (n = 1), and hemoptysis (n=1).

Permanently discontinue RETEVMO in patients with severe or life-threatening hemorrhage *[see Dosage and Administration (2.5)]*.

5.6 Hypersensitivity

Hypersensitivity occurred in 6% of patients receiving RETEVMO, including Grade 3 hypersensitivity in 1.9%. The median time to onset was 1.9 weeks (range: 5 days to 2 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminitis.

If hypersensitivity occurs, withhold RETEVMO and begin corticosteroids at a dose of 1 mg/kg prednisone (or equivalent). Upon resolution of the event, resume RETEVMO at a reduced dose and increase the dose of RETEVMO by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity *[see Dosage and Administration (2.5)]*. Continue steroids until patient reaches target dose and then taper. Permanently discontinue RETEVMO for recurrent hypersensitivity.

5.7 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) occurred in 0.6% of patients with medullary thyroid carcinoma receiving RETEVMO *[see Adverse Reactions (6.1)]*. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

5.8 Risk of Impaired Wound Healing

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, RETEVMO has the potential to adversely affect wound healing.

Withhold RETEVMO for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of RETEVMO after resolution of wound healing complications has not been established.

5.9 Hypothyroidism

RETEVMO can cause hypothyroidism. Hypothyroidism occurred in 13% of patients treated with RETEVMO; all reactions were Grade 1 or 2. Hypothyroidism occurred in 13% of patients (50/373) with thyroid cancer and 13% of patients (53/423) with other solid tumors including NSCLC *[see Adverse Reactions (6.1)]*.

Monitor thyroid function before treatment with RETEVMO and periodically during treatment. Treat with thyroid hormone replacement as clinically indicated. Withhold RETEVMO until clinically stable or permanently discontinue RETEVMO based on severity *[see Dosage and Administration (2.5)]*.

5.10 Embryo-Fetal Toxicity

Based on data from animal reproduction studies and its mechanism of action, RETEVMO can cause fetal harm when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryolethality and malformations.

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the last dose.

Advise males with female partners of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hepatotoxicity *[see Warnings and Precautions (5.1)]*
- Interstitial Lung Disease / Pneumonitis *[see Warnings and Precautions (5.2)]*
- Hypertension *[see Warnings and Precautions (5.3)]*
- QT Interval Prolongation *[see Warnings and Precautions (5.4)]*
- Hemorrhagic Events *[see Warnings and Precautions (5.5)]*
- Hypersensitivity *[see Warnings and Precautions (5.6)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.7)]*
- Risk of Impaired Wound Healing *[see Warnings and Precautions (5.8)]*
- Hypothyroidism *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

RET Gene Fusion or Gene Mutation Positive Solid Tumors

The pooled safety population described in the WARNINGS and PRECAUTIONS and below reflects exposure to RETEVMO as a single agent at 160 mg orally twice daily evaluated in 796 patients with advanced solid tumors in LIBRETTO-001 *[see Clinical Studies (14)]*. Among the 796 patients who received RETEVMO, 84% were exposed for 6 months or longer and 73% were exposed for greater than one year. Among these patients, 96% received at least one dose of RETEVMO at the recommended dosage of 160 mg orally twice daily.

The median age was 59 years (range: 15 to 92 years); 0.3% were pediatric patients 12 to 16 years of age; 51% were male; and 69% were White, 23% were Asian, 5% were Hispanic/Latino, and 3% were Black. The most common tumors were NSCLC (45%), MTC (40%), and non-medullary thyroid carcinoma (7%).

Serious adverse reactions occurred in 44% of patients who received RETEVMO. The most frequent serious adverse reactions (≥2% of patients) were pneumonia, pleural effusion, abdominal pain, hemorrhage, hypersensitivity, dyspnea, and hyponatremia. Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions included sepsis (n = 6), respiratory failure (n = 5), hemorrhage (n = 4), pneumonia (n = 3), pneumonitis (n = 2), cardiac arrest (n=2), sudden death (n = 1), and cardiac failure (n = 1).

Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received RETEVMO. Adverse reactions resulting in permanent discontinuation in ≥0.5% of patients included increased ALT (0.6%), fatigue (0.6%), sepsis (0.5%), and increased AST (0.5%).

Dosage interruptions due to an adverse reaction occurred in 64% of patients who received RETEVMO. Adverse reactions requiring dosage interruption in ≥5% of patients included increased ALT, increased AST, diarrhea, and hypertension.

Dose reductions due to an adverse reaction occurred in 41% of patients who received RETEVMO. Adverse reactions requiring dosage reductions in ≥2% of patients included increased ALT, increased AST, QT prolongation, fatigue, diarrhea, drug hypersensitivity, and edema.

The most common adverse reactions (≥25%) were edema, diarrhea, fatigue, dry mouth, hypertension, abdominal pain, constipation, rash, nausea, and headache.

The most common Grade 3 or 4 laboratory abnormalities (≥5%) were decreased lymphocytes, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), decreased sodium, and decreased calcium.

Table 5 summarizes the adverse reactions in LIBRETTO-001.

Table 5: Adverse Reactions (≥20%) in Patients Who Received RETEVMO in LIBRETTO-001

Adverse Reaction	RETEVMO (n = 796)	
	Grades 1-4# (%)	Grades 3-4 (%)
Gastrointestinal		
Diarrhea[1]	47	5*
Dry Mouth	43	0
Abdominal pain[2]	34	2.5*
Constipation	33	0.8*
Nausea	31	1.1*
Vomiting	22	1.8*
Vascular		
Hypertension	41	20
General		
Edema[3]	49	0.8*
Fatigue[4]	46	3.1*
Arthralgia	21	0.3*
Skin		
Rash[5]	33	0.6*
Nervous System		
Headache[6]	28	1.4*
Respiratory		
Cough[7]	24	0
Dyspnea[8]	22	3.1
Investigations		
Prolonged QT interval	21	4.8*
Blood and Lymphatic System		
Hemorrhage[9]	22	2.6

1 Diarrhea includes diarrhea, defecation urgency, frequent bowel movements, gastrointestinal hypermotility, anal incontinence.

2 Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness, epigastric discomfort, gastrointestinal pain.

3 Edema includes edema, edema peripheral, face edema, periorbital edema, eye edema, eyelid edema, orbital edema, localized edema, lymphedema, scrotal edema, peripheral swelling, scrotal swelling, swelling, swelling face, eye swelling, generalized edema, genital edema.

4 Fatigue includes fatigue, asthenia, malaise.

5 Rash includes rash, rash erythematous, rash macular, rash maculopapular, rash morbilliform, rash papular, rash pruritic, butterfly rash, exfoliative rash, rash follicular, rash generalized, rash vesicular.

6 Headache includes headache, sinus headache, tension headache.

7 Includes cough, productive cough, upper airway cough syndrome.

8 Includes dyspnea, dyspnea exertional, dyspnea at rest.

9 Hemorrhage includes hemorrhage, epistaxis, hematuria, hemoptysis, contusion, rectal hemorrhage, vaginal hemorrhage, ecchymosis, hematochezia, petechiae, traumatic hematoma, anal hemorrhage, blood blister, blood urine present, cerebral hemorrhage, gastric hemorrhage, hemorrhage intracranial, hemorrhage subcutaneous, spontaneous hematoma, abdominal wall hematoma, angina bullosa hemorrhagica, conjunctival hemorrhage, disseminated intravascular coagulation, diverticulum intestinal hemorrhagic, eye hemorrhage, gastrointestinal hemorrhage, gingival bleeding, hematemesis, hemorrhagic stroke, hemorrhoidal hemorrhage, hepatic hemorrhage, hepatic hematoma, intraabdominal hemorrhage, laryngeal hemorrhage, lower gastrointestinal hemorrhage, melena, mouth hemorrhage, occult blood positive, post procedural hemorrhage,

postmenopausal hemorrhage, pelvic hematoma, periorbital hematoma, periorbital hemorrhage, pharyngeal hemorrhage, pulmonary contusion, purpura, retinal hemorrhage, retroperitoneal hematoma, scleral hemorrhage, skin hemorrhage, subarachnoid hemorrhage, subdural hemorrhage, upper gastrointestinal hemorrhage, uterine hemorrhage, vessel puncture site hematoma.

* Only includes a grade 3 adverse reaction.

Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03

Clinically relevant adverse reactions in ≤15% of patients who received RETEVMO include hypothyroidism (13%); hypersensitivity (6%); interstitial lung disease/pneumonitis, chylothorax, chylous ascites or tumor lysis syndrome (all < 2%).

Table 6 summarizes the laboratory abnormalities in LIBRETTO-001.

Table 6: Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received RETEVMO in LIBRETTO-001

Laboratory Abnormality	RETEVMO[1]	
	Grades 1-4[#] (%)	Grades 3-4 (%)
Chemistry		
Increased AST	59	11
Decreased calcium	59	5.7
Increased ALT	56	12
Decreased albumin	56	2.3
Increased glucose	53	2.8
Increased creatinine	47	2.4
Decreased sodium	42	11
Increased alkaline phosphatase	40	3.4
Increased total cholesterol	35	1.7
Increased potassium	34	2.7
Decreased glucose	34	1.0
Decreased magnesium	33	0.6
Increased bilirubin	30	2.8
Hematology		
Decreased lymphocytes	52	20
Decreased platelets	37	3.2
Decreased hemoglobin	28	3.5
Decreased neutrophils	25	3.2

[1] Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 765 to 791 patients.

Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03

Increased Creatinine

In healthy subjects administered RETEVMO 160 mg orally twice daily, serum creatinine increased 18% after 10 days. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed *[see Clinical Pharmacology (12.3)]*.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on RETEVMO

Acid-Reducing Agents

Concomitant use of RETEVMO with acid-reducing agents decreases selpercatinib plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may reduce RETEVMO anti-tumor activity.

Avoid concomitant use of PPIs, H2 receptor antagonists, and locally-acting antacids with RETEVMO. If coadministration cannot be avoided, take RETEVMO with food (with a PPI) or modify its administration time (with a H2 receptor antagonist or a locally-acting antacid) *[see Dosage and Administration (2.4)]*.

Strong and Moderate CYP3A Inhibitors

Concomitant use of RETEVMO with a strong or moderate CYP3A inhibitor increases selpercatinib plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the risk of RETEVMO adverse reactions, including QTc interval prolongation.

Avoid concomitant use of strong and moderate CYP3A inhibitors with RETEVMO. If concomitant use of strong and moderate CYP3A inhibitors cannot be avoided, reduce the RETEVMO dosage and monitor the QT interval with ECGs more frequently *[see Dosage and Administration (2.6), Warning and Precautions (5.4)]*.

Strong and Moderate CYP3A Inducers

Concomitant use of RETEVMO with a strong or moderate CYP3A inducer decreases selpercatinib plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may reduce RETEVMO anti-tumor activity.

Avoid coadministration of strong or moderate CYP3A inducers with RETEVMO.

7.2 Effects of RETEVMO on Other Drugs

CYP2C8 and CYP3A Substrates

RETEVMO is a moderate CYP2C8 inhibitor and a weak CYP3A inhibitor. Concomitant use of RETEVMO with CYP2C8 and CYP3A substrates increases their plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of RETEVMO with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

Certain P-gp Substrates

RETEVMO is a P-gp inhibitor. Concomitant use of RETEVMO with P-gp substrates increases their plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of RETEVMO with P-gp substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for P-gp substrates provided in their approved product labeling.

7.3 Drugs that Prolong QT Interval

RETEVMO is associated with QTc interval prolongation *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.2)]*. Monitor the QT interval with ECGs more frequently in patients who require treatment with concomitant medications known to prolong the QT interval.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies, and its mechanism of action *[see Clinical Pharmacology (12.1)]*, RETEVMO can cause fetal harm when administered to a pregnant woman. There are no available data on RETEVMO use in pregnant women to inform drug-associated risk. Administration of selpercatinib to pregnant rats during the period of organogenesis resulted in embryolethality and malformations at maternal exposures that were approximately equal to the human exposure at the clinical dose of 160 mg twice daily. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Selpercatinib administration to pregnant rats during the period of organogenesis at oral doses ≥100 mg/kg [approximately 3.6 times the human exposure based on the area under the curve (AUC) at the clinical dose of 160 mg twice daily] resulted in 100% post-implantation loss. At the dose of 50 mg/kg [approximately equal to the human exposure (AUC) at the clinical dose of 160 mg twice daily], 6 of 8 females had 100% early resorptions; the remaining 2 females had high levels of early resorptions with only 3 viable fetuses across the 2 litters. All viable fetuses had decreased fetal body weight and malformations (2 with short tail and one with small snout and localized edema of the neck and thorax).

8.2 Lactation

Risk Summary

There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with RETEVMO and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

Based on animal data, RETEVMO can cause embryolethality and malformations at doses resulting in exposures less than or equal to the human exposure at the clinical dose of 160 mg twice daily *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating RETEVMO *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the last dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the last dose.

Infertility

RETEVMO may impair fertility in females and males of reproductive potential *[see Use in Specific Populations (8.4), Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of RETEVMO have been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced *RET* fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate). Use of RETEVMO for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.2, 14.3)]*. The safety and effectiveness of RETEVMO have not been established in these indications in patients less than 12 years of age.

The safety and effectiveness of RETEVMO have not been established in pediatric patients for other indications *[see Indications and Usage (1)]*.

Juvenile Animal Toxicity Data

In a juvenile rat toxicity study, animals were dosed daily with selpercatinib from post-natal day 21 to day 70 (approximately equivalent to a human child to late adolescent). Selpercatinib increased physeal thickness of multiple bones, extending into the metaphysis and associated with decreased trabecular bone, which was not reversible at doses approximately equivalent to or greater than the adult human exposure at the clinical dose of 160 mg twice daily. Growth plate changes were associated with impairment of bone modeling, resulting in decreased femur length and with reduction in bone mineral density. Selpercatinib also induced reversible hypocellularity of bone marrow in males at ≥30 mg/kg (approximately equivalent to or greater than the adult human exposure at the clinical dose of 160 mg twice daily), and reversible alterations of dentin composition at ≥50 mg/kg (approximately 3 times the adult human exposure at the clinical dose of 160 mg twice daily). Irreversible, dose-dependent degeneration of testicular germinal epithelium, with vacuolation of Sertoli cells and corresponding depletion of spermatozoa in the epididymides, was also observed at ≥ 30 mg/kg

(approximately equivalent to or greater than the adult human exposure at the clinical dose of 160 mg twice daily) and affected male reproductive performance at 50 mg/kg (approximately 3 times the adult human exposure at the clinical dose of 160 mg twice daily). Females exhibited delay in attainment of vaginal patency, a marker of sexual maturity, at 125 mg/kg (approximately 4 times the adult human exposure at the clinical dose of 160 mg twice daily); this affect was associated with lower mean body weight. Similar effects in irregular thickening of growth plates in adult rats and minipigs, and tooth dysplasia and malocclusion, resulting in tooth loss in adult rats were observed in repeat dose studies of up to 13-week duration with selpercatinib.

Monitor growth plates in adolescent patients with open growth plates. Consider interrupting or discontinuing therapy based on the severity of any growth plate abnormalities and based on an individual risk-benefit assessment.

8.5 Geriatric Use

Of 796 patients who received RETEVMO, 34% (268 patients) were ≥65 years of age and 9% (74 patients) were ≥75 years of age. No overall differences were observed in the safety or effectiveness of RETEVMO between patients who were ≥65 years of age and younger patients.

8.6 Renal Impairment

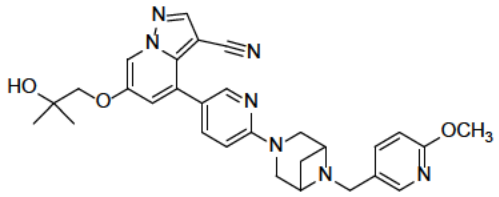
No dosage modification is recommended for patients with mild to severe renal impairment [estimated Glomerular Filtration Rate (eGFR) ≥15 to 89 mL/min, estimated by Modification of Diet in Renal Disease (MDRD) equation]. The recommended dosage has not been established for patients with end-stage renal disease (ESRD) *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Reduce the dose when administering RETEVMO to patients with severe [total bilirubin greater than 3 to 10 times upper limit of normal (ULN) and any AST] hepatic impairment *[see Dosage and Administration (2.7)]*. No dosage modification is recommended for patients with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST) or moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST) hepatic impairment. Monitor for RETEVMO-related adverse reactions in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Selpercatinib is a kinase inhibitor. The molecular formula for selpercatinib is $C_{29}H_{31}N_7O_3$ and the molecular weight is 525.61 g/mol. The chemical name is 6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-((6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. Selpercatinib has the following chemical structure:



Selpercatinib is a white to light yellow powder that is slightly hygroscopic. The aqueous solubility of selpercatinib is pH dependent, from sparingly soluble at low pH to practically insoluble at neutral pH.

RETEVMO (selpercatinib) is supplied as 40 mg or 80 mg hard gelatin capsules for oral use. Each capsule contains inactive ingredients of microcrystalline cellulose and colloidal silicon dioxide. The 40 mg capsule shell is composed of gelatin, titanium dioxide, ferric oxide black and black ink. The 80 mg capsule shell is composed of gelatin, titanium dioxide, FD&C blue #1 and black ink. The black ink is composed of shellac, potassium hydroxide and ferric oxide black.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Selpercatinib is a kinase inhibitor. Selpercatinib inhibited wild-type RET and multiple mutated RET isoforms as well as VEGFR1 and VEGFR3 with IC_{50} values ranging from 0.92 nM to 67.8 nM. In other enzyme assays, selpercatinib also inhibited FGFR 1, 2, and 3 at higher concentrations that were still clinically achievable. In cellular assays, selpercatinib

inhibited RET at approximately 60-fold lower concentrations than FGFR1 and 2 and approximately 8-fold lower concentration than VEGFR3.

Certain point mutations in *RET* or chromosomal rearrangements involving in-frame fusions of *RET* with various partners can result in constitutively activated chimeric RET fusion proteins that can act as oncogenic drivers by promoting cell proliferation of tumor cell lines. In in vitro and in vivo tumor models, selpercatinib demonstrated anti-tumor activity in cells harboring constitutive activation of RET proteins resulting from gene fusions and mutations, including CCDC6-RET, KIF5B-RET, RET V804M, and RET M918T. In addition, selpercatinib showed anti-tumor activity in mice intracranially implanted with a patient-derived *RET* fusion positive tumor.

12.2 Pharmacodynamics

Exposure-Response Relationship

Selpercatinib exposure-response relationships and the time course of pharmacodynamic response have not been fully characterized.

Cardiac Electrophysiology

The effect of RETEVMO on the QTc interval was evaluated in a thorough QT study in healthy subjects. The largest mean increase in QTc is predicted to be 10.6 msec (upper 90% confidence interval: 12.1 msec) at the mean steady-state maximum concentration (C_{max}) observed in patients after administration of 160 mg twice daily. The increase in QTc was concentration-dependent.

12.3 Pharmacokinetics

The pharmacokinetics of selpercatinib were evaluated in patients with locally advanced or metastatic solid tumors administered 160 mg twice daily unless otherwise specified. Steady state selpercatinib AUC and C_{max} increased in a slightly greater than dose proportional manner over the dose range of 20 mg once daily to 240 mg twice daily [0.06 to 1.5 times the maximum recommended total daily dosage].

Steady-state was reached by approximately 7 days and the median accumulation ratio after administration of 160 mg twice daily was 3.4-fold. Mean steady-state selpercatinib [coefficient of variation (CV%)] C_{max} was 2,980 (53%) ng/mL and AUC_{0-24h} was 51,600 (58%) ng*h/mL.

Absorption

The median t_{max} of selpercatinib is 2 hours. The mean absolute bioavailability of RETEVMO capsules is 73% (60% to 82%) in healthy subjects.

Effect of Food

No clinically significant differences in selpercatinib AUC or C_{max} were observed following administration of a high-fat meal (approximately 900 calories, 58 grams carbohydrate, 56 grams fat and 43 grams protein) in healthy subjects.

Distribution

The apparent volume of distribution (V_{ss}/F) of selpercatinib is 191 L.

Protein binding of selpercatinib is 96% in vitro and is independent of concentration. The blood-to-plasma concentration ratio is 0.7.

Elimination

The apparent clearance (CL/F) of selpercatinib is 6 L/h in patients and the half-life is 32 hours following oral administration of RETEVMO in healthy subjects.

Metabolism

Selpercatinib is metabolized predominantly by CYP3A4. Following oral administration of a single radiolabeled 160 mg dose of selpercatinib to healthy subjects, unchanged selpercatinib constituted 86% of the radioactive drug components in plasma.

Excretion

Following oral administration of a single radiolabeled 160 mg dose of selpercatinib to healthy subjects, 69% of the administered dose was recovered in feces (14% unchanged) and 24% in urine (12% unchanged).

Specific Populations

The apparent volume of distribution and clearance of selpercatinib increase with increasing body weight (27 kg to 179 kg).

No clinically significant differences in the pharmacokinetics of selpercatinib were observed based on age (15 years to 92 years), sex, or mild, moderate, or severe renal impairment (eGFR ≥15 to 89 mL/min). The effect of ESRD on selpercatinib pharmacokinetics has not been studied.

Patients with Hepatic Impairment

The selpercatinib $AUC_{0\text{-}INF}$ increased by 7%, 32%, and 77% in subjects with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST), moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST), and severe (total bilirubin greater than 3 to 10 times ULN and any AST) hepatic impairment, respectively, compared to subjects with normal hepatic function.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Proton-Pump Inhibitors (PPI): Coadministration with multiple daily doses of omeprazole (PPI) decreased selpercatinib $AUC_{0\text{-}INF}$ and C_{max} when RETEVMO was administered fasting. Coadministration with multiple daily doses of omeprazole did not significantly change the selpercatinib $AUC_{0\text{-}INF}$ and C_{max} when RETEVMO was administered with food (Table 7).

Table 7: Change in Selpercatinib Exposure After Coadministration with PPI

	Selpercatinib $AUC_{0\text{-}INF}$	**Selpercatinib C_{max}**
RETEVMO fasting	Reference	Reference
RETEVMO fasting + PPI	↓ 69%	↓ 88%
RETEVMO with a high-fat meal[1] + PPI	↑ 2%	↓ 49%
RETEVMO with a low-fat meal[2] + PPI	No change	↓ 22%

[1] High-fat meal: approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively; approximately 800 to 1,000 calories total.

[2] Low-fat meal: approximately 390 calories and 10 g of fat.

H2 Receptor Antagonists: No clinically significant differences in selpercatinib pharmacokinetics were observed when coadministered with multiple daily doses of ranitidine (H2 receptor antagonist) given 10 hours prior to and 2 hours after the RETEVMO dose (administered fasting).

Strong CYP3A Inhibitors: Coadministration of multiple doses of itraconazole (strong CYP3A inhibitor) increased the selpercatinib $AUC_{0\text{-}INF}$ by 133% and C_{max} by 30%.

Moderate CYP3A Inhibitors: Coadministration of multiple doses of diltiazem, fluconazole, or verapamil (moderate CYP3A inhibitors) is predicted to increase the selpercatinib AUC by 60-99% and C_{max} by 46-76%.

Strong CYP3A Inducers: Coadministration of multiple doses of rifampin (strong CYP3A inducer) decreased the selpercatinib $AUC_{0\text{-}INF}$ by 87% and C_{max} by 70%.

Moderate CYP3A Inducers: Coadministration of multiple doses of bosentan or efavirenz (moderate CYP3A inducers) is predicted to decrease the selpercatinib AUC by 40-70% and C_{max} by 34-57%.

Weak CYP3A Inducers: Coadministration of multiple doses of modafinil (weak CYP3A inducer) is predicted to decrease the selpercatinib AUC by 33% and C_{max} by 26%.

CYP2C8 Substrates: Coadministration of RETEVMO with repaglinide (sensitive CYP2C8 substrate) increased the repaglinide $AUC_{0\text{-}INF}$ by 188% and C_{max} by 91%.

CYP3A Substrates: Coadministration of RETEVMO with midazolam (sensitive CYP3A substrate) increased the midazolam $AUC_{0\text{-}INF}$ by 54% and C_{max} by 39%.

P-glycoprotein (P-gp) Substrates: Coadministration of RETEVMO with dabigatran (P-gp substrate) increased the dabigatran $AUC_{0\text{-}INF}$ by 38% and C_{max} by 43%.

P-gp Inhibitors: No clinically significant differences in selpercatinib pharmacokinetics were observed when coadministered with a single dose of rifampin (P-gp inhibitor).

MATE1 Substrates: No clinically significant differences in glucose levels were observed when metformin (MATE1 substrate) was coadministered with selpercatinib.

In Vitro Studies

CYP Enzymes: Selpercatinib does not inhibit or induce CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations.

Transporter Systems: Selpercatinib inhibits MATE1 and BCRP, but does not inhibit OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BSEP, and MATE2-K at clinically relevant concentrations. Selpercatinib may increase serum creatinine by decreasing renal tubular secretion of creatinine via inhibition of MATE1 *[see Adverse Effects (6.1)]*. Selpercatinib is a substrate for P-gp and BCRP, but not for OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with selpercatinib. Selpercatinib was not mutagenic in the in vitro bacterial reverse mutation (Ames) assays, with or without metabolic activation, or clastogenic in the in vitro micronucleus assay in human peripheral lymphocytes, with or without metabolic activation. Selpercatinib was positive in the in vivo micronucleus assay in rats at concentrations >7 times the C_{max} at the human dose of 160 mg twice daily.

In general toxicology studies, male rats and minipigs exhibited testicular degeneration which was associated with luminal cell debris and/or reduced luminal sperm in the epididymis at selpercatinib exposures approximately 0.4 (rat) and 0.1 (minipig) times the clinical exposure by AUC at the recommended human dose. In a dedicated fertility study in male rats, administration of selpercatinib at doses up to 30 mg/kg/day (approximately twice the clinical exposure by AUC at the 160 twice daily dose) for 28 days prior to cohabitation with untreated females did not affect mating or have clear effects on fertility. Males did, however, display a dose-dependent increase in testicular germ cell depletion and spermatid retention at doses ≥3 mg/kg (~0.2 times the clinical exposure by AUC at the 160 twice daily dose) accompanied by altered sperm morphology at 30 mg/kg.

In a dedicated fertility study in female rats treated with selpercatinib for 15 days before mating to Gestational Day 7, there were decreases in the number of estrous cycles at a dose of 75 mg/kg (approximately equal to the human exposure by AUC at the 160 mg twice daily clinical dose). While selpercatinib did not have clear effects on mating performance or ability to become pregnant at any dose level, half of females at the 75 mg/kg dose level had 100% nonviable embryos. At the same dose level in females with some viable embryos there were increases in post-implantation loss. In a 3-month general toxicology study in minipigs, there were findings of decreased or absent corpora lutea at a selpercatinib dose of 15 mg/kg (approximately 0.3 times to the human exposure by AUC at the 160 mg twice daily clinical dose). Corpora luteal cysts were present in the minipig at selpercatinib doses ≥2 mg/kg (approximately 0.07 times the human exposure by AUC at the 160 mg twice daily clinical dose).

14 CLINICAL STUDIES

14.1 *RET* Fusion-Positive Non-Small Cell Lung Cancer

The efficacy of RETEVMO was evaluated in patients with advanced *RET* fusion-positive NSCLC enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001, NCT03157128). The study enrolled patients with advanced or metastatic *RET* fusion-positive NSCLC who had progressed on platinum-based chemotherapy and patients with locally advanced (stage III who were not candidates for surgical resection or definitive chemoradiation) or metastatic NSCLC without prior systemic therapy in separate cohorts. Identification of a *RET* gene alteration was prospectively determined in local laboratories using next generation sequencing (NGS), polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH) or other local testing methods. Adult patients received RETEVMO 160 mg orally twice daily until unacceptable toxicity or disease progression; patients enrolled in the dose escalation phase were permitted to adjust their dose to 160 mg twice daily. The major efficacy outcome measures were confirmed overall response rate (ORR) and duration of response (DOR), as determined by a blinded independent review committee (BIRC) according to RECIST v1.1.

RET Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy

Efficacy was evaluated in 247 patients with *RET* fusion-positive NSCLC previously treated with platinum chemotherapy enrolled into a cohort of LIBRETTO-001.

The median age was 61 years (range: 23 to 81); 57% were female; 44% were White, 48% were Asian, 4.9% were Black, and 2.8% were Hispanic/Latino. ECOG performance status was 0-1 (97%) or 2 (3%) and 97% of patients had metastatic disease. Patients received a median of 2 prior systemic therapies (range 1–15); 58% had prior anti-PD-1/PD-L1 therapy.

RET fusions were detected in 94% of patients using NGS (84.6% tumor samples; 9.3% blood or plasma samples), 4.0% using FISH, 1.6% using PCR and 0.4% by other local testing methods.

Efficacy results for previously treated *RET* fusion-positive NSCLC are summarized in Table 8.

Table 8: Efficacy Results in LIBRETTO-001 (*RET* Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy)

	RETEVMO (n = 247)
Overall Response Rate[1] (95% CI)	61% (55%, 67%)
Complete response	7.3%
Partial response	54%
Duration of Response	
Median in months (95% CI)	28.6 (20, NE)
% with ≥ 12 months[2]	63%

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NE = not estimable

For the 144 patients who received an anti-PD-1 or anti-PD-L1 therapy, either sequentially or concurrently with platinum-based chemotherapy, an exploratory subgroup analysis of ORR was 63% (95% CI: 54%, 70%) and the median DOR was 28.6 months (95% CI: 14.8, NE).

Among the 247 patients with previously treated *RET* fusion-positive NSCLC, 16 had measurable CNS metastases at baseline as assessed by BIRC. One patient received radiation therapy (RT) to the brain within 2 months prior to study entry. Responses in intracranial lesions were observed in 14 of these 16 patients; 39% of responders had an intracranial DOR of ≥ 12 months.

Treatment-naïve *RET* Fusion-Positive NSCLC

Efficacy was evaluated in 69 patients with treatment-naïve *RET* fusion-positive NSCLC enrolled into a cohort of LIBRETTO-001.

The median age was 63 years (range 23 to 92); 62% were female; 70% were White, 19% were Asian, and 6% were Black. ECOG performance status was 0-1 (94%) or 2 (6%) and 99% of patients had metastatic disease. *RET* fusions were detected in 91% of patients using NGS (60.9% tumor samples; 30.4% in blood), 7.2% using FISH and 1.4% using PCR.

Efficacy results for treatment naïve *RET* fusion-positive NSCLC are summarized in Table 9.

Table 9: Efficacy Results in LIBRETTO-001 (Treatment-Naïve *RET* Fusion-Positive NSCLC)

	RETEVMO (n =69)
Overall Response Rate[1] (95% CI)	84% (73%, 92%)
Complete response	5.8%
Partial response	78%
Duration of Response	
Median in months (95% CI)	20.2 (13, NE)
% with ≥ 12 months[2]	50%

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NE = not estimable

Among the 69 patients with treatment-naïve *RET* fusion-positive NSCLC, 5 had measurable CNS metastases at baseline as assessed by BIRC. Two patients received RT to the brain within 2 months prior to study entry. Responses in intracranial lesions were observed in 4 of these 5 patients; 38% of responders had an intracranial DOR of ≥ 12 months.

14.2 *RET*-Mutant Medullary Thyroid Cancer

The efficacy of RETEVMO was evaluated in patients with *RET*-mutant MTC enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001, NCT03157128). The study enrolled patients with advanced or metastatic *RET*-mutant MTC who had been previously treated with cabozantinib or vandetanib (or both) and patients with advanced or metastatic *RET*-mutant MTC who were naïve to cabozantinib and vandetanib in separate cohorts.

RET-Mutant MTC Previously Treated with Cabozantinib or Vandetanib

Efficacy was evaluated in 55 patients with *RET*-mutant advanced MTC who had previously treated with cabozantinib or vandetanib enrolled into a cohort of LIBRETTO-001.

The median age was 57 years (range: 17 to 84); 66% were male; 89% were White, 7% were Hispanic/Latino, and 1.8% were Black. ECOG performance status was 0-1 (95%) or 2 (5%) and 98% of patients had metastatic disease. Patients received a median of 2 prior systemic therapies (range 1 – 8). *RET* mutation status was detected in 82% of patients using NGS (78% tumor samples; 4% blood or plasma), 16% using PCR, and 2% using an unknown test. The protocol excluded patients with synonymous, frameshift or nonsense *RET* mutations; the specific mutations used to identify and enroll patients are described in Table 10.

Table 10: Mutations used to Identify and Enroll Patients with *RET*-Mutant MTC in LIBRETTO-001

RET Mutation Type[1]	Previously Treated (n = 55)	Cabozantinib/ Vandetanib Naïve (n = 88)	Total (n = 143)
M918T	33	49	82
Extracellular cysteine mutation[2]	7	20	27
V804M or V804L	5[4]	6	11
Other[3]	10	13	23

[1] Somatic or germline mutations; protein change.

[2] Extracellular cysteine mutations involving cysteine residues 609, 611, 618, 620, 630, and 634.

[3] Other included: K666N (1), D631_L633delinsV (2), D631_L633delinsE (5), D378_G385delinsE (1), D898_E901del (2), A883F (4), E632_L633del (4), L790F (2), T636_V637insCRT(1), D898_E901del + D903_S904delinsEP (1).

[4] One patient also had a M918T mutation.

Efficacy results for *RET*-mutant MTC are summarized in Table 11.

Table 11: Efficacy Results in LIBRETTO-001 (*RET*-Mutant MTC Previously Treated with Cabozantinib or Vandetanib)

	RETEVMO (n = 55)
Overall Response Rate[1] (95% CI)	69% (55%, 81%)
Complete response	9%
Partial response	60%
Duration of Response	
Median in months (95% CI)	NE (19.1, NE)
% with ≥6 months[2]	76

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NE = not estimable

Cabozantinib and Vandetanib-naïve *RET*-Mutant MTC

Efficacy was evaluated in 88 patients with *RET*-mutant MTC who were cabozantinib and vandetanib treatment-naïve enrolled into a cohort of LIBRETTO-001.

The median age was 58 years (range: 15 to 82) with two patients (2.3%) aged 12 to 16 years; 66% were male; and 86% were White, 4.5% were Asian, and 2.3% were Hispanic/Latino. ECOG performance status was 0-1 (97%) or 2 (3.4%). All patients (100%) had metastatic disease and 18% had received 1 or 2 prior systemic therapies (including 8% kinase inhibitors, 4.5% chemotherapy, 2.3% anti-PD1/PD-L1 therapy, and 1.1% radioactive iodine). *RET* mutation status was detected in 77.3% of patients using NGS (75.0% tumor samples; 2.3% blood samples), 18.2% using PCR, and 4.5% using an unknown test. The mutations used to identify and enroll patients are described in Table 10.

Efficacy results for cabozantinib and vandetanib-naïve *RET*-mutant MTC are summarized in Table 12.

Table 12: Efficacy Results in LIBRETTO-001 (Cabozantinib and Vandetanib-naïve *RET*-Mutant MTC)

	RETEVMO (n = 88)
Overall Response Rate[1] (95% CI)	73% (62%, 82%)
Complete response	11%
Partial response	61%
Duration of Response	
Median in months (95% CI)	22.0 (NE, NE)
% with ≥6 months[2]	61

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NE = not estimable

14.3 *RET* Fusion-Positive Thyroid Cancer

The efficacy of RETEVMO was evaluated in patients with advanced *RET* fusion-positive thyroid cancer enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001, NCT03157128). Efficacy was evaluated in 27 patients with *RET* fusion-positive thyroid cancer who were radioactive iodine (RAI)-refractory (if RAI was an appropriate treatment option) and were systemic therapy naïve and patients with *RET* fusion-positive thyroid cancer who were RAI-refractory and had received sorafenib, lenvatinib, or both, in separate cohorts.

The median age was 54 years (range 20 to 88); 52% were male; 74% were White, 11% were Hispanic/Latino, 7.4% were Asian, and 3.7% were Black. ECOG performance status was 0-1 (89%) or 2 (11%). All (100%) patients had metastatic disease with primary tumor histologies including papillary thyroid cancer (78%), poorly differentiated thyroid cancer (11%), anaplastic thyroid cancer (7%) and Hurthle cell thyroid cancer (4%). Patients had received a median of 3 prior therapies (range 1–7). *RET* fusion-positive status was detected in 93% of patients using NGS tumor samples and in 7% using blood samples.

Efficacy results for *RET* fusion-positive thyroid cancer are summarized in Table 13.

Table 13: Efficacy Results in LIBRETTO-001 (*RET* Fusion-Positive Thyroid Cancer)

	RETEVMO Previously Treated (n = 19)	**RETEVMO Systemic Therapy Naïve (n = 8)**
Overall Response Rate[1] (95% CI)	79% (54%, 94%)	100% (63%, 100%)
Complete response	5.3%	12.5%
Partial response	74%	88%
Duration of Response		
Median in months (95% CI)	18.4 (7.6, NE)	NE (NE, NE)
% with ≥6 months[2]	87	75

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NE = not estimable

14.4 Other *RET* Fusion-Positive Solid Tumors

The efficacy of RETEVMO was evaluated in patients with locally advanced or metastatic *RET* fusion-positive solid tumors enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001, NCT03157128). Efficacy was evaluated in 41 patients with *RET* fusion-positive tumors other than NSCLC and thyroid cancer with disease progression on or following prior systemic treatment or who had no satisfactory alternative treatment options.

The median age was 50 years (range 21 to 85), 54% were female, 68% were White, 24% were Asian, and 4.9% were Black; 7% were Hispanic/Latino. ECOG performance status was 0-1 (95%) or 2 (5%) and 95% of patients had metastatic disease. Thirty-seven patients (90%) received prior systemic therapy (median 2 [range 0 – 9]; 32% received 3 or more). The most common cancers were pancreatic adenocarcinoma (27%), colorectal (24%), salivary (10%) and unknown primary (7%). *RET* fusion-positive status was detected in 97.6% of patients using NGS and 2.4% using FISH.

Efficacy results for *RET* fusion-positive solid tumors other than NSCLC and thyroid cancer are summarized in Table 14 and Table 15.

Table 14: Efficacy Results in LIBRETTO-001 (Other *RET* Fusion-Positive Solid Tumors)

	RETEVMO (n = 41)
Overall Response Rate[1] (95% CI)	44% (28, 60)
Complete response	4.9%
Partial response	39%
Duration of Response	
Median in months (95% CI)	24.5 (9.2, NE)
% with ≥6 months[2]	67%

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NE = not estimable

Table 15: Efficacy Results by Tumor Type in LIBRETTO-001 (Other *RET* Fusion-Positive Solid Tumors)

Tumor Type	**Patients (n = 41)**	**ORR**[1,2]		**DOR Range (months)**
		n (%)	**95% CI**	
Pancreatic adenocarcinoma	11	6 (55%)	(23, 83)	2.5, 38.3+
Colorectal	10	2 (20%)	(2.5, 56)	5.6, 13.3
Salivary	4	2 (50%)	(7, 93)	5.7, 28.8+
Unknown primary	3	1 (33%)	(0.8, 91)	9.2
Breast	2	PR, CR	NA	2.3+, 17.3
Sarcoma (soft tissue)	2	PR, SD	NA	14.9+
Xanthogranuloma	2	NE, NE	NA	NA
Carcinoid (bronchial)	1	PR	NA	24.1+
Carcinoma of the skin	1	NE	NA	NA
Cholangiocarcinoma	1	PR	NA	5.6+
Ovarian	1	PR	NA	14.5+
Pulmonary carcinosarcoma	1	NE	NA	NA
Rectal neuroendocrine	1	NE	NA	NA

Small intestine	1	CR	NA	24.5

+ denotes ongoing response.

[1] Confirmed overall response rate assessed by BIRC.

[2] Best overall response for each patient is presented for tumor types with ≤2 patients.

CI = confidence interval, CR = complete response, DOR = duration of response, NA = not applicable, NE = not evaluable, ORR = overall response rate, PR = partial response, SD = stable disease.

16 HOW SUPPLIED/STORAGE AND HANDLING

RETEVMO (selpercatinib) capsules are supplied as follows:

40 mg: Gray opaque, imprinted with “Lilly”, “3977” and “40 mg” in black ink

60 count bottle NDC 0002-3977-60

80 mg: Blue opaque, imprinted with “Lilly”, “2980” and “80 mg” in black ink

60 count bottle NDC 0002-2980-60

120 count bottle NDC 0002-2980-26

Store at 20°C to 25°C (68°F to 77°F); excursions between 15°C and 30°C (59°F to 86°F) are permitted [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hepatotoxicity

Advise patients that hepatotoxicity can occur and to immediately contact their healthcare provider for signs or symptoms of hepatotoxicity *[see Warnings and Precautions (5.1)]*.

Interstitial Lung Disease (ILD)/Pneumonitis

Advise patients that ILD/ pneumonitis can occur and to contact their healthcare provider immediately for signs or symptoms of ILD including new or worsening cough or shortness of breath *[see Warnings and Precautions (5.2)]*.

Hypertension

Advise patients that they will require regular blood pressure monitoring and to contact their healthcare provider if they experience symptoms of increased blood pressure or elevated readings *[see Warnings and Precautions (5.3)]*.

QT Prolongation

Advise patients that RETEVMO can cause QTc interval prolongation and to inform their healthcare provider if they have any QTc interval prolongation symptoms, such as syncope *[see Warnings and Precautions (5.4)]*.

Hemorrhagic Events

Advise patients that RETEVMO may increase the risk for bleeding and to contact their healthcare provider if they experience any signs or symptoms of bleeding [*see Warnings and Precautions (5.5)]*.

Hypersensitivity Reactions

Advise patients to monitor for signs and symptoms of hypersensitivity reactions, particularly during the first month of treatment *[see Warnings and Precautions (5.6)]*.

Tumor Lysis Syndrome

Advise patients to contact their healthcare provider promptly to report any signs and symptoms of TLS *[see Warnings and Precautions (5.7)]*.

Risk of Impaired Wound Healing

Advise patients that RETEVMO may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure *[see Warnings and Precautions (5.8)]*.

Hypothyroidism

Advise patients that RETEVMO can cause hypothyroidism and to immediately contact their healthcare provider for signs or symptoms of hypothyroidism *[see Warnings and Precautions (5.9)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the possible risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.10), Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during the treatment with RETEVMO and for 1 week after the last dose *[see Use in Specific Populations (8.3)]*.

Advise males with female partners of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with RETEVMO and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males and females of reproductive potential that RETEVMO may impair fertility *[see Use in Specific Populations (8.4), Nonclinical Toxicology (13.1)]*.

Drug Interactions

Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid St. John's wort, proton pump inhibitors, H2 receptor antagonists, and antacids while taking RETEVMO.

If PPIs are required, instruct patients to take RETEVMO with food. If H2 receptor antagonists are required, instruct patients to take RETEVMO 2 hours before or 10 hours after the H2 receptor antagonist. If locally-acting antacids are required, instruct patients to take RETEVMO 2 hours before or 2 hours after the locally-acting antacid *[see Drug Interactions (7.1, 7.2)]*.

Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

A6.01-RET-0002-USPI-20220921

PATIENT INFORMATION
RETEVMO® (reh-TEHV-moh)
(selpercatinib)
capsules

What is RETEVMO?

RETEVMO is a prescription medicine that is used to treat certain cancers caused by abnormal *RET* genes in:

- adults with locally advanced non-small cell lung cancer (NSCLC) or NSCLC that has spread.
- adults and children 12 years of age and older with advanced medullary thyroid cancer (MTC) or MTC that has spread, who require a medicine by mouth or injection (systemic therapy).
- adults and children 12 years of age and older with advanced thyroid cancer or thyroid cancer that has spread who require a medicine by mouth or injection (systemic therapy), and who have received radioactive iodine and it did not work or is no longer working.
- adults with locally advanced solid tumors (cancers) or solid tumors that have spread, and have gotten worse (progressed) on or after other treatment or there are no satisfactory treatment options.

Your healthcare provider will perform a test to make sure that RETEVMO is right for you.

It is not known if RETEVMO is safe and effective when used:

- in children younger than 12 years of age for the treatment of MTC who require systemic therapy, and advanced thyroid cancer who require systemic therapy and who have received radioactive iodine and it did not work or is no longer working, **or**
- in children for the treatment of any other cancers.

Before taking RETEVMO, tell your healthcare provider about all your medical conditions, including if you:

- have liver problems
- have lung or breathing problems other than lung cancer
- have high blood pressure
- have heart problems including a condition called QT prolongation
- have bleeding problems
- plan to have surgery. You should stop taking RETEVMO at least 7 days before your planned surgery. See **"What are the possible side effects of RETEVMO?"**
- are pregnant or plan to become pregnant. RETEVMO can harm your unborn baby. You should not become pregnant during treatment with RETEVMO.
  - If you are able to become pregnant, your healthcare provider will do a pregnancy test before you start treatment with RETEVMO.
  - **Females who are able to become pregnant** should use effective birth control (contraception) during treatment and for **1 week** after your last dose of RETEVMO. Talk to your healthcare provider about birth control methods that may be right for you.
  - Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with RETEVMO.
  - **Males with female partners who are able to become pregnant** should use effective birth control during treatment with RETEVMO and for **1 week** after your last dose of RETEVMO.
- are breastfeeding or plan to breastfeed. It is not known if RETEVMO passes into your breast milk. Do not breastfeed during treatment with RETEVMO and for 1 week after your last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. RETEVMO may affect the way other medicines work, and other medicines may affect how RETEVMO works, and may increase your risk of side effects.

You should avoid taking St. John's wort, proton pump inhibitors (PPIs such as dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole sodium, rabeprazole), H2 blockers (such as famotidine, nizatidine, and cimetidine), and antacids that contain aluminum, magnesium, calcium, simethicone, or buffered medicines during treatment with RETEVMO. If you cannot avoid taking PPIs, H2 blockers, or antacids, see "**How should I take RETEVMO**?" for more information on how to take RETEVMO with these medicines.
Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take RETEVMO?

- Take RETEVMO exactly as your healthcare provider tells you.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with RETEVMO if you have side effects. Do not change your dose or stop taking RETEVMO unless your healthcare provider tells you.
- RETEVMO is taken by mouth, usually 2 times a day about 12 hours apart.
- Take RETEVMO with or without food.
- If you take a proton-pump inhibitor (PPIs such as dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole sodium, and rabeprazole), take RETEVMO with food.

- If you take an antacid that contains aluminum, magnesium, calcium, simethicone, or buffered medicines, take RETEVMO 2 hours before or 2 hours after taking the antacid.
- If you take an H2 blocker (such as famotidine, nizatidine, and cimetidine), take RETEVMO 2 hours before or 10 hours after taking the H2 blocker.
- Swallow RETEVMO capsules whole. Do not crush or chew the capsules.
- If you vomit after taking a dose of RETEVMO, do not take an extra dose. Take the next dose of RETEVMO at your scheduled time.
- Do not take a missed dose of RETEVMO unless it is more than 6 hours until your next scheduled dose.

What are the possible side effects of RETEVMO?

RETEVMO may cause serious side effects, including:

- **Liver problems.** Liver problems (increased liver enzymes) are common with RETEVMO and may sometimes be serious. Your healthcare provider will do blood tests before and during treatment with RETEVMO to check for liver problems. Tell your healthcare provider right away if you get any of the following symptoms of liver problems during treatment:
  - yellowing of your skin or the white part of your eyes (jaundice)
  - dark "tea-colored" urine
  - sleepiness
  - bleeding or bruising
  - loss of appetite
  - nausea or vomiting
  - pain on the upper right side of your stomach area
- **Lung problems.** RETEVMO may cause severe or life-threatening inflammation of the lungs during treatment, that can lead to death. Tell your healthcare provider right away if you have any new or worsening lung symptoms, including:
  - shortness of breath
  - cough
  - fever
- **High blood pressure (hypertension).** High blood pressure is common with RETEVMO and may sometimes be severe. You should check your blood pressure regularly during treatment with RETEVMO. If you develop blood pressure problems, your healthcare provider may prescribe medicine to treat your high blood pressure. Tell your healthcare provider if you have increased blood pressure readings or get any symptoms of high blood pressure, including:
  - confusion
  - headaches
  - shortness of breath
  - dizziness
  - chest pain
- **Heart rhythm changes (QT prolongation).** RETEVMO may cause very slow, very fast or irregular heartbeats. Your healthcare provider may perform tests before and during treatment with RETEVMO to check the activity of your heart and the levels of body salts (electrolytes) and thyroid-stimulating hormone (TSH) in your blood. Tell your healthcare provider right away if you get any of the following symptoms:
  - loss of consciousness
  - fainting
  - dizziness
  - a change in the way your heart beats (heart palpitations)
- **Bleeding problems.** RETEVMO can cause bleeding which can be serious and may lead to death. Tell your healthcare provider if you have any signs of bleeding during treatment with RETEVMO, including:
  - vomiting blood or if your vomit looks like coffee-grounds
  - pink or brown urine
  - red or black (looks like tar) stools
  - coughing up blood or blood clots
  - unusual bleeding or bruising of your skin
  - menstrual bleeding that is heavier than normal
  - unusual vaginal bleeding
  - nose bleeds that happen often
  - drowsiness or difficulty being awakened
  - confusion
  - headache
  - change in speech
- **Allergic reactions.** RETEVMO can cause a fever, rash, muscle or joint pain, especially during the first month of treatment. Tell your healthcare provider if you get any of these symptoms.
- **Tumor lysis syndrome (TLS).** TLS is caused by a fast breakdown of cancer cells. TLS can cause kidney failure, the need for dialysis treatment, and an abnormal heartbeat. TLS can lead to hospitalization. Your healthcare provider may do blood tests to check you for TLS. You should stay well hydrated during treatment with RETEVMO. Call your healthcare provider or get emergency medical help right away if you develop any of these symptoms during treatment with RETEVMO:
  - nausea
  - vomiting
  - weakness
  - swelling
  - shortness of breath
  - muscle cramps
  - seizures

- **Risk of wound healing problems.** Wounds may not heal properly during treatment with RETEVMO. Tell your healthcare provider if you plan to have any surgery before or during treatment with RETEVMO.
  - You should stop taking RETEVMO at least 7 days before planned surgery.
  - Your healthcare provider should tell you when you may start taking RETEVMO again after surgery.
- **Low thyroid hormone levels in your blood (hypothyroidism).** Your healthcare provider will do blood tests to check your thyroid function before and during treatment with RETEVMO. Tell your healthcare provider right away if you develop signs or symptoms of low thyroid hormone levels, including:
  - weight gain
  - feeling cold
  - tiredness that worsens or that does not go away
  - constipation

The most common side effects of RETEVMO include:

- swelling of your arms, legs, hands, and feet (edema)
- diarrhea
- tiredness
- dry mouth
- high blood pressure
- stomach-area (abdominal) pain
- constipation
- rash
- nausea
- headache

The most common severe abnormal laboratory test results with RETEVMO include decreased white blood cell count, decreased levels of sodium in the blood, and decreased levels of calcium in the blood.

RETEVMO may affect fertility in females and males, which may affect your ability to have children. Talk to your healthcare provider if this is a concern for you.

These are not all the possible side effects with RETEVMO.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store RETEVMO?

- Store RETEVMO capsules at room temperature between 68°F to 77°F (20°C to 25°C).

Keep RETEVMO and all medicines out of the reach of children.

General information about the safe and effective use of RETEVMO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use RETEVMO for a condition for which it was not prescribed. Do not give RETEVMO to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for more information about RETEVMO that is written for health professionals.

What are the ingredients in RETEVMO?

Active ingredient: selpercatinib

Inactive ingredients: microcrystalline cellulose, colloidal silicon dioxide. The 40 mg capsule shell contains: gelatin, titanium dioxide, ferric oxide black and black ink. The 80 mg capsule shell contains: gelatin, titanium dioxide, FD&C blue #1 and black ink. The black ink contains: shellac, potassium hydroxide and ferric oxide black.

Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

B0.3.01-RET-000X-PPI-20220921

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 09/2022

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213246Orig1s008

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	sNDA (supplemental NDA)
Application Number(s)	213246 (S-8)
Priority or Standard	Priority
Submit Date(s)	May 31, 2022
Received Date(s)	May 31, 2022
PDUFA Goal Date	November 30, 2022
Division/Office	Division of Oncology 2 / Office of Oncologic Drugs
Review Completion Date	*Electronic stamp date*
Established Name	selpercatinib
Trade Name	RETEVMO
Pharmacologic Class	Kinase inhibitor
Code name	LOXO-292
Applicant	Loxo Oncology Inc., a wholly owned subsidiary of Eli Lilly and Company
Formulation(s)	Capsules: 40 mg, 80 mg
Dosing Regimen	Patients 50 kg or greater: 160 mg orally twice daily Less than 50 kg: 120 mg orally twice daily
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s)	Adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{0-24}	area under the plasma concentration curve from time 0 to 24 hours
BID	twice daily
BLA	biologics license application
BOR	best overall response
CBR	clinical benefit rate
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
COA	clinical outcome assessment
CSR	clinical study report
DCR	disease control rate
DOR	duration of response
ECG	electrocardiogram
eCTD	electronic common technical document
JZJA	LIBRETTO-001
IRC	independent review committee
LIBRETTO-001	first-in-human, clinical Phase 1/2 study for selpercatinib
MedDRA	Medical Dictionary for Regulatory Activities
MTC	medullary thyroid cancer
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSCLC	non-small cell lung cancer
ObsRO	observed reported outcome
ORR	objective response rate
OS	overall survival
PD	pharmacodynamics
PDTC	poorly differentiated thyroid cancer
PFS	progression-free survival
PK	pharmacokinetics
PerfO	performance outcome
PR	partial response
PREA	pediatric research equity act

PRO	patient reported outcome
PTC	papillary thyroid cancer
SAE	serious adverse event
SAP	statistical analysis plan
RANO	Response Assessment in Neuro-Oncology Criteria
RECIST	Response Evaluation Criteria in Solid Tumors
RET	rearranged-during transfection
TC	thyroid cancer
TEAE	treatment emergent adverse event

1 Executive Summary

Product Introduction

Selpercatinib is an oral inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase as well as vascular endothelial growth factor receptors 1 and 3 (VEFGR1 and VEGFR3). Gene rearrangements (fusions) in *RET* have the potential to be oncogenic drivers and have been observed in a variety of tumor types.

Selpercatinib was granted accelerated approval in May 2020 for the treatment of adult patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC), as well as adult and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant medullary thyroid cancer who require systemic therapy and adult and pediatric patients 12 years of age and older with advanced or metastatic *RET* fusion-positive thyroid cancer (TC) who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

The recommended dosage regimen is selpercatinib 160 mg orally twice daily for patients 50 kg or greater; for patients less than 50 kg, the recommended dosage is 120 mg orally twice daily.

Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness supporting the accelerated approval of selpercatinib under 21 CFR part 314 subpart H, for the treatment of adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.

The recommendation for accelerated approval is based on results from Study LOXO-RET-17001 (LIBRETTO-001), an international, single-arm, dose-escalation and expansion study of selpercatinib in patients with advanced solid tumors with *RET* alterations. The primary efficacy population included 41 patients with locally advanced or metastatic *RET* fusion-positive solid tumors other than NSCLC and thyroid cancer that had progressed on or following prior systemic treatment or who had no satisfactory alternative treatment options. The recommendation for approval is supported by results from LIBRETTO-001 in patients with *RET* fusion-positive NSCLC and thyroid cancer, which formed the basis of the prior approvals in these tumor types.

The confirmed overall response rate (ORR) per RECIST 1.1 as determined by blinded independent review committee (BIRC) was 44% (95% Confidence Interval [CI] 28, 60). The median duration of response (DOR) was 24.5 months (95% CI 9.2, not evaluable [NE]), with 67%

(95% CI 41, 87) and 56% (95% 31, 56) remaining in response at 6 and 12 months, respectively. Patients with 10 of 14 tumor types with a variety of fusion partners had objective responses by BIRC, including patients with the following tumors: pancreatic adenocarcinoma, colorectal, salivary, unknown primary, breast, soft tissue sarcoma, bronchial carcinoid, ovarian, small intestine, and cholangiocarcinoma. Patients were enrolled at sites distributed across multiple geographic regions (North America, Asia Pacific, Europe, and Middle East), including 63% of patients enrolled in the United States, ensuring that the results are largely applicable to the intended U.S. population.

The submitted evidence meets the statutory evidentiary standard for accelerated approval. An ORR of sufficient magnitude and duration is an endpoint reasonably likely to predict clinical benefit in patients with solid tumors, and this endpoint has supported the accelerated approvals of multiple other targeted therapies for patients with solid tumors harboring oncogenic driver mutations. The review team considers that the durable responses observed across multiple tumor types in Study LIBRETTO-001, in the setting of a genetically-based biologic rationale and the existing evidence supporting approvals in advanced *RET* fusion-positive NSCLC and thyroid cancer, provide evidence of a clinically meaningful benefit of selpercatinib in the rare, genetically defined subgroup of patients with locally advanced or metastatic *RET* fusion-positive solid tumors. The Applicant has agreed to a postmarketing requirement to provide data on ORR and DOR in additional patients with advanced or metastatic solid tumors with *RET* fusions other than NSCLC or thyroid cancer treated with selpercatinib to verify and describe the clinical benefit of selpercatinib across tumor types, particularly in tumor types for which responses are not well characterized.

This is the first approval of a targeted therapy for patients with *RET* fusion-positive solid tumors other than NSCLC and thyroid cancer. When considered in the context of the route of administration and its safety profile, the ORR and durable responses observed with selpercatinib are reasonably likely to predict clinical benefit and provide a meaningful advantage over available treatments for these patients.

Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

RET gene fusions are rare oncogenic alterations observed most commonly in patients with papillary thyroid cancer (5-10%) and non-small cell lung cancer (NSCLC; 1-2%) (Li et al, 2019; Subbiah et al, 2020). In other solid tumors, *RET* gene fusions are observed in <1% of patients, but are a distinct population given they are typically mutually exclusive of other oncogenic drivers (Belli et al, 2020;). Due to the rarity of *RET* fusions in solid tumors other than NSCLC and thyroid cancer, there is limited knowledge regarding differences in prognosis attributable to the presence of *RET* fusions. However, for most patients with advanced solid tumors that have progressed on or following prior systemic treatment, prognosis is poor. Five-year overall survival for the most common solid tumors which are diagnosed at a distant stage ranges from 3 to 40% (Siegel et al, 2021).

Selpercatinib is an oral inhibitor of the RET receptor tyrosine kinase. The recommended dosage regimen is 160 mg orally twice daily for patients weighing 50 kg or greater, and 120 mg orally twice daily for patients < 50 kg. Support for this application is based on safety and efficacy data from Study LOXO-RET-17001 (LIBRETTO-001), an international, single-arm, dose-escalation and expansion study of selpercatinib in patients with advanced solid tumors including *RET* fusion-positive solid tumors. The analysis population included patients who demonstrated a protocol-defined *RET* fusion identified based on a CLIA-certified (or equivalent) test with measurable disease per RECIST version 1.1, and received one or more doses of selpercatinib. Patients were required to have locally advanced or metastatic disease which had progressed on or were intolerant to ≥1 prior standard therapy, or no standard therapy existed, or the patient declined standard therapy.

The primary efficacy analysis population included 41 patients with 14 different tumor types other than NSCLC and thyroid cancer, including the following tumor types: pancreatic adenocarcinoma, colorectal, salivary gland, unknown primary, breast, sarcoma, xanthogranuloma, carcinoid (bronchial), ovarian, small intestine, cholangiocarcinoma, pulmonary carcinosarcoma, rectal neuroendocrine and carcinoma of the skin. There are no targeted therapies approved for these *RET* fusion-positive solid tumors. Available therapies in the second line or later for each of these tumor types per NCCN guidelines are variable, but most are chemotherapy-based with response rates generally < 30%.

The confirmed ORR per RECIST 1.1 as determined by BIRC was 44% (95% CI 28, 60) with median DOR 24.5 months (95% CI 9.2, NE). The observed proportion of patients remaining in response per BIRC was 67% (95% CI 41, 87) at 6 months and 56% (95% 31, 56) at 12 months,

respectively. Patients with 10 of 14 tumor types with a variety of fusion partners had objective responses by BIRC, including patients with the following tumors: pancreatic, colorectal, salivary, unknown primary, breast, soft tissue sarcoma, bronchial carcinoid, ovarian, small intestine, and cholangiocarcinoma. The evidence in 41 patients provided in this application suggests that treatment with selpercatinib results in durable responses across tumor types; evidence in favor of a tissue agnostic indication also relies upon the robust response rates and durable responses observed in patients with NSCLC and thyroid cancer with RET fusions in LIBRETTO-001, which formed the basis of the original approval of selpercatinib. There is some uncertainty regarding the magnitude of responses expected in extremely rare tumor types represented in the efficacy population and in tumor types not represented in the efficacy population. In addition, there is uncertainty as to why the response rate observed in patients with colorectal cancer is lower than other tumors. However, considering the lack of available treatment options for these patients, strength of the scientific evidence across other tumor types, and acceptable safety profile of selpercatinib in this setting, the totality of the evidence favors approval for a tissue agnostic indication. Data from additional patients to confirm clinical benefit across tumor types will be submitted as a post-marketing requirement.

The primary safety population included 796 patients treated with selpercatinib in Study LIBRETTO-001. The most common (≥25%) treatment-emergent adverse events (TEAEs) were edema, diarrhea, fatigue, dry mouth, hypertension, abdominal pain, constipation, rash, nausea, and headache. The most common (≥5%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), decreased sodium, and decreased calcium. No new safety signals were identified during this review. However, the safety sections of the USPI were updated during review of supplemental application #7 (S7), the review period for which overlaps with this supplement. Refer to the clinical review for S7 for details regarding safety updates.

The clinical review team determined that it is in the best interest of U.S. patients to approve selpercatinib for the treatment of *RET* fusion positive solid tumors before one or more companion diagnostic assays are ready for PMA submission. The Applicant has agreed to a post-marketing commitment (PMC) to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a companion diagnostic test to identify patients who may benefit from selpercatinib.

The submitted evidence in this supplemental NDA meets the statutory evidentiary standard for accelerated approval. Given the rarity of *RET* fusion-positive solid tumors and the magnitude of response observed in patients with NSCLC and thyroid cancer, a randomized trial was not feasible. The durable responses observed across multiple tumor types in Study LIBRETTO-001, in the setting of a genetically-based biologic rationale and the existing approvals in advanced *RET* fusion-positive NSCLC and thyroid cancer, provide evidence of a clinically meaningful benefit of selpercatinib in the rare, genetically defined subgroup of patients with locally advanced or metastatic *RET* fusion-positive solid

tumors. Based on the favorable risk-benefit assessment for this population with a serious, life-threatening disease, accelerated approval is recommended for the following indication:

> Selpercatinib (RETEVMO) is indicated for the treatment of adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.

The recommended dose is based on weight as follows:
For patients 50 kg or greater, the recommended dosage is 160 mg orally twice daily; for patients less than 50 kg, the recommended dosage is 120 mg orally twice daily.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• *RET* gene fusions are somatic alterations which lead to formation of distinct *RET* oncoproteins (Li et al, 2019; Kato et al, 2017). • *RET* fusions are observed in <1% of patients with solid tumors other than NSCLC and thyroid cancer (Belli et al, 2020; Li et al, 2019; Subbiah et al, 2020). • The rarity of these tumors limits knowledge of alteration-specific prognosis, but survival is poor for most patients with advanced solid tumors that have progressed on or following prior systemic treatment, with 5-year OS ranging from 3 to 40% (Siegel et al, 2021).	Advanced *RET* fusion-positive solid tumors are a rare group of life-threatening malignancies with poor survival.
Current Treatment Options	• There are no approved therapies for *RET* fusion-positive solid tumors other than NSCLC and thyroid cancer. • Selpercatinib and pralsetinib are selective oral RET inhibitors that were granted accelerated approval in 2020 for patients with *RET*	There is an unmet medical need for patients with locally advanced or metastatic *RET* fusion-positive solid tumors that have progressed on or following prior systemic treatment or who

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	fusion-positive NSCLC and thyroid cancer. • Treatment options for patients with advanced *RET* fusion-positive solid tumors who have progressed on prior therapy are the same as those used for patients without a specific driver mutation, although the effectiveness of these treatments has not specifically studied in this subpopulation. • For advanced solid tumors, second line or greater therapies per NCCN guidelines vary by tumor type and are generally chemotherapy-based with overall responses rates < 30%.	have no satisfactory alternative treatment options. This conclusion is based on the observed ORRs, DORs, and overall survival (OS) reported for therapies currently used in clinical practice for the treatment of this patient population.
Benefit	• The primary efficacy data supporting this sNDA are from Study LOXO-RET-17001 (LIBRETTO-001), an international, single-arm, dose-escalation and expansion study of selpercatinib in patients with advanced solid tumors with RET alterations. • The primary efficacy population included 41 patients with locally advanced or metastatic RET fusion-positive solid tumors other than NSCLC and thyroid cancer that had progressed on or following prior systemic treatment or who had no satisfactory alternative treatment options. • The confirmed ORR per RECIST 1.1 as determined by BIRC was 44% (95% CI 28, 60) with median DOR 24.5 months (95% CI 9.2, NE). • The observed proportion of patients remaining in response per BIRC was 67% (95% CI 41, 87) at 6 months and 56% (95% 31, 56) at 12 months, respectively. • Patients with 10 of 14 tumor types with a variety of fusion partners had objective responses by BIRC, including patients with the following tumors: pancreatic adenocarcinoma, colorectal, salivary, unknown	The submitted evidence meets the statutory evidentiary standard for accelerated approval. The observed ORR, along with the observed duration of responses, in the setting of a genetically-based biologic rationale and the existing approvals in advanced *RET* fusion-positive NSCLC and thyroid cancer, are clinically meaningful in the context of the poor prognosis of the disease and the limited available approved therapies. The Applicant will submit data from the ongoing clinical trial to describe ORR and DOR in additional patients with advanced or metastatic solid tumors other than NSCLC and thyroid cancer with a *RET* gene fusion as a post

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	primary, breast, soft tissue sarcoma, bronchial carcinoid, ovarian, small intestine, and cholangiocarcinoma.	marketing requirement.
Risk and Risk Management	• The primary safety population included 796 patients treated with selpercatinib in Study LIBRETTO-001. • The most common (≥25%) treatment-emergent adverse events (TEAEs) were edema, diarrhea, fatigue, dry mouth, hypertension, abdominal pain, constipation, rash, nausea, and headache. • The most common (≥5%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), decreased sodium, and decreased calcium. • No new safety signals were identified during this review. • Although development of a companion diagnostic to identify patients with advanced or metastatic solid tumors with *RET* gene fusions for treatment with selpercatinib is ongoing, a companion diagnostic is not currently approved.	The observed safety profile is acceptable in the context of the treatment of a life-threatening disease and is overall consistent with the known adverse effects of selpercatinib. Although selpercatinib can cause serious toxicities, these safety concerns are adequately addressed by information in the product labeling. Selpercatinib will be prescribed by oncologists who know how to monitor, identify, and manage the toxicities described in the USPI; therefore, the risk mitigation strategies included in the label are considered sufficient and a REMS was not considered necessary for the safe use of selpercatinib. The Applicant has agreed to a postmarketing commitment to conduct studies needed to analytically and clinically validate an in vitro diagnostic device for use in selection of patients with advanced or metastatic solid tumors with *RET* gene fusions.

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application, include:	Refer to original multidisciplinary review, Section 8.2.7.
	□ Clinical outcome assessment (COA) data, such as	
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.	

X

Cross-Disciplinary Team Leader

Diana Bradford, MD

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2 Therapeutic Context

Analysis of Condition

RET can become oncogenically activated by 2 primary mechanisms: 1) fusions (chromosomal rearrangements that fuse the RET kinase domain with a partner protein dimerization domain, which lead to ligand-independent, constitutive activity) and 2) point mutations and insertions and deletions, which directly or indirectly activate the kinase. *RET* gene fusions occur most commonly in lung cancer (~1% to 2% of NSCLCs), PTCs, and PDTCs (~5% to 10% of PTCs and PDTCs), and in extremely rare subsets of other cancers, including breast, colon, esophageal, ovarian, prostate, stomach, pancreatic, salivary gland cancers, and sarcomas (most occurring at rates of <1%) (GENIE cBIO Portal, Kato et al. 2017; Davis et al. 2020; Kohno et al. 2020; Santoro et al. 2020).
Multiple lines of evidence suggest that *RET* fusions are activating genomic events leading to oncogenic addiction regardless of the tumor type in which they arise. *RET* fusions cause transformation in vitro and in vivo and promote cell proliferation and survival when expressed in human cancer cell lines. They also display the hallmark feature of oncogene addiction—their inhibition in *RET*-fusion, patient-derived cancer models leads to tumor cell death. These characteristics and effects have been observed for *RET* fusions in both in vitro and in vivo models for a range of tumor types, including thyroid, lung, colorectal, pancreatic, and breast cancers, as well as mammary adenocarcinomas and melanoma (Takahashi et al. 1985; Portella 1996; Ohshima et al. 2010; Matsubara et al. 2012; Saito et al. 2014; Stransky et al. 2014; Drilon et al. 2018; Gozgit et al. 2018; Paratala et al. 2018; Subbiah et al. 2018). Consistent with this observation, *RET* fusions in tumors identified from patients almost always appear mutually exclusive of other known validated oncogenic drivers, a pattern shared by other bona fide cancer drivers (Farago and Azzioli 2017).

Benefit of selpercatinib against RET fusion-driven tumors
Selpercatinib has demonstrated potent in vitro and in vivo activity as a selective inhibitor of both wild-type and oncogenically activated RET, including RET fusions and RET mutations. Selpercatinib treatment resulted in significant cytotoxicity only in human cancer cell lines that harbor endogenous RET gene alterations (e.g., fusions and mutations), with minimal cytotoxicity in human cancer cell lines without an endogenous RET gene alteration, as expected for a highly specific inhibitor of RET.
LIBRETTO-001 (J2G-OX-JZJA) is an ongoing multicenter, multi-cohort, open-label, dose-escalation, dose-expansion study in patients 12 years or older with advanced solid tumors, including RET fusion-positive solid tumors, RET-mutant medullary thyroid cancer (MTC), and other tumors with RET activation.

Data from LIBRETTO 001 supported the approval of selpercatinib by the FDA on 08 May 2020 for

- adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC
- adult and pediatric patients ≥12 years of age with advanced or metastatic RET mutant MTC who require systemic therapy, and
- adult and pediatric patients ≥12 years of age with advanced or metastatic RET fusion positive thyroid cancer (TC) who require systemic therapy and who are radioactive iodine refractory (if radioactive iodine is appropriate).

Each of these indications was approved under accelerated approval based on ORR and DOR results.

Clinically, selpercatinib demonstrated benefit in patients in LIBRETTO-001 with NSCLC and multiple histologies of TC regardless of *RET* fusion partner. The efficacy seen irrespective of fusion partner improves the likelihood of observing efficacy in a diversity of cancer histologies. Based on the available nonclinical data and the known mechanism of action and clinical findings demonstrated with selpercatinib, it is the sponsor's position that structural rearrangements leading to inframe *RET* gene fusions, and leading to constitutive *RET* activation, drive oncogenic addiction regardless of the cancer type in which they arise and should therefore respond to treatment with selpercatinib.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. RET is a transmembrane glycoprotein receptor-tyrosine kinase that is encoded by the *RET* (rearranged during transfection) proto-oncogene located on chromosome 10 (Drilon et al, 2018). *RET* gene fusions are a type of somatic mutation leading to formation of distinct *RET* oncoproteins and are observed across multiple solid tumors with a variety of fusion partners (Li et al, 2019; Kato et al, 2017). The American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) cancer registry reported *RET* fusion is present in 0.36% of AACR GENIE cases, with lung adenocarcinoma, thyroid gland papillary carcinoma, colon adenocarcinoma, poorly differentiated thyroid gland carcinoma, and breast invasive ductal carcinoma having the greatest prevalence (AACR Project GENIE Consortium, 2017).

Given the rarity of *RET* fusions in solid tumors other than NSCLC and thyroid cancer, there is limited knowledge regarding differences in prognosis due to the presence of *RET* fusions. However, for most patients with advanced solid tumors that have progressed on or following prior systemic treatment, prognosis is poor. Five-year overall survival for the most common solid tumors which are diagnosed at a distant stage ranges from 3 to 40% (Siegel et al, 2021).

Analysis of Current Treatment Options

Patients with other advanced or metastatic *RET* fusion-positive solid tumors (e.g., colorectal, pancreatic, and salivary gland cancers) may have established and/or approved standards of care in early treatment lines. However, the 5-year survival rate for advanced disease is typically less than 10% and treatment options are often nontargeted and chemotherapy-based, can have suboptimal efficacy and high rates of toxicity, and typically become scarce and ineffective beyond first- and second-line care (Son et al. 2018; Chiorean et al. 2020; Howlader et al. 2020; NCCN 2020; Sohal et al. 2020).

Table 2.1 shows response rates for available, standard treatment options, as per NCCN guidelines, for *RET* fusion-positive tumor types applicable to this sNDA. Included are tumor types occuring at a 1% or greater frequency in the cBIO database (GENIE cBIO Portal) and solid tumors, other than NSCLC and TC, in LIBRETTO-001 which occurred in 2 patients or more.

In most cases, by the time a patient reaches second-line treatment, response rates to available therapy are generally <20%, highlighting the unmet medical need for these patients. There are no available targeted treatment options specifically for patients with these RET fusion-positive cancers, irrespective of line of treatment.

Table 2-1. Treatment Effect for Representative Standard-of-Care Therapies in Tumor Types That Have Been Shown to Harbor *RET* Fusions Excluding NSCLC and TC Tumors

Cancer Type	Line of Therapy	Treatment	N	Response Rate (%) (95% CI[a])	Time to Event Endpoints	Reference
Colorectal	1L	FOLFOX + bevacizumab	53	68% (53.8, 92)	mDOR: 8 mo	Emmanouilides et al. 2007
		CAPEOX + bevacizumab	699[b]	38%	mDOR: 8.5 mo mPFS: 9.4 mo	Saltz et al. 2008
		FOLFIRI	144	47.2%	mPFS: 7.6 mo	Fuchs et al. 2007
	2L	Irinotecan	132	12% (7.0, 18.1)	NR	Camptosar package insert, 2022
	3L	FOLFIRI	33	6% (0, 13)	mPFS: 18 wk	Andre et al. 1999
	3L+	Regorafenib	505	1%	mPFS 1.9 mo	Grothey et al. 2013

Cancer Type	Line of Therapy	Treatment	N	Response Rate (%) (95% CI[a])	Time to Event Endpoints	Reference
Pancreas	1L	FOLFIRINOX	171	32% (24.7, 39.1)	mDOR: 5.9 mo mPFS: 6.4 mo	Conroy et al. 2011
		Gemcitabine + nab-paclitaxel	431	23% (19, 27)	mDOT: 3.9 mo mPFS: 5.5 mo	Von Hoff et al. 2013
	2L	5-FU + nanoliposomal irinotecan post gemcitabine	117	16%	mPFS: 3.1 mo	Wang-Gillam et al. 2016
		Gemcitabine + nab-paclitaxel post FOLFIRINOX	30	13% (5.3, 29.7)	mPFS: 3.8 mo	Mita et al. 2019
Salivary	1L	Cisplatin + doxorubicin + cyclophosphamide	15	60%	NR	Debaere et al. 2011
		Cisplatin + vinorelbine	40	35% (22.1, 50.4)	mPFS: 6.3 mo	Hong et al. 2017
	2L	No standard				
Unknown primary	1L	Carboplatin + paclitaxel	75	39% (27.5, 49.9)	mDOR: 6 mo	Briasoulis et al. 2000
		Cisplatin + gemcitabine	27	19%	mPFS: 5 mo	Gross-Goupil et al. 2012
	2L	No standard				
Breast	1L, HER2-	Doxorubicin	165	33% (40.1, 55.5)	mTTP: 21 weeks	Chan et al. 1999
	1L, HER2+	Pertuzumab + trastuzumab + docetaxel	402	80%	mPFS: 18.5 mo	Baselga et al. 2012
	2L, HER2-	Paclitaxel	212	22% (15.4, 27.5)	mTTP: 4.7 mo	Perez et al. 2001
	2L, HER2+	Ado-trastuzumab emtansine	495	44% (38.6, 48.6)	mPFS: 9.6 mo	Verma et al. 2012
	3L+, HER2-	Vinorelbine	40	25% (13, 41)	mDOR: 6 mo	Zelek et al. 2001

Cancer Type	Line of Therapy	Treatment	N	Response Rate (%) (95% CI[a])	Time to Event Endpoints	Reference
Sarcoma (soft tissue)	1L	Doxorubicin	251	18% (13.5, 23.1)	mPFS: 6.8 mo	Tap et al. 2020
	≥2L	Pazopanib	246	6%	mPFS: 4.6 mo	van der Graaf et al. 2012
Xanthogranuloma	No standard[c]					
	1L	Methotrexate + cytarabine	83	88% (includes multiple histiocytic diseases)	3-year EFS: 68.0%	Cao et al. 2020
Biliary tract cancers	1L	Gemcitabine + cisplatin	161	26%	mPFS: 8.0 mo 2L	Valle et al. 2010
	2L	FOLFOX	81	NA	mOS: 6.2 mo	Lamarca et al. 2019
		FOLFIRI	12	0%	mPFS: 1.7 mo	Caparica et al. 2019
Non-melanoma skin	No standard					
Esophagogastric	1L, HER2+	Trastuzumab + cisplatin + capecitabine OR 5FU	294	47% (NR)	mDOR 6.9 mo (6, 8)	Bang 2010
	1L, HER2-	Nivolumab + capecitabine/ oxaliplatin OR 5FU/oxaliplatin	378	60% (55, 65)	mDOR 9.5 mo (8.0-11.4)	Janjigian 2021
	2L, HER2+	Trastuzumab deruxtecan	119	43% (34,52)	mDOR 11.3 mo (5.6, NE)	Shitara 2020
	2L, HER2-	Ramucirumab + paclitaxel	330	28% (23, 33)	mDOR 4.4 mo (2.8, 7.5)	Wilke 2014

Cancer Type	Line of Therapy	Treatment	N	Response Rate (%) (95% CI[a])	Time to Event Endpoints	Reference
Brain[d]	2L	Temozolomide, anaplastic astrocytoma	162	35% (NR)	mPFS 5.4 mo (NR)	Yung 1999
		Temozolomide glioblastoma	14 53	14% (NR) 15% (NR)	6 mo PFS 57% mPFS 11.0 mo (4.5, 9.45)	Chamberlain 2009
		Bevacizumab, anaplastic astrocytoma	25	64% (45, 83)	mPFS 7 mo (4.5, 9.45)	Chamberlain 2009
		Bevacizumab + irinotecan, glioblastoma	82	37.8% (26.5, 50.8)	mPFS 5.6 mo (4.4, 6.2)	Friedman 2009

Abbreviations: 1L =
1L = first line; 2L = second line; 3L = third line; 5-FU = fluorouracil; CAPEOX = capecitabine + oxaliplatin; CI = confidence interval; EFS = event-free survival; FOLFIRI = 5-FU + folinic acid + irinotecan; FOLFOX = folinic acid + 5-FU + oxaliplatin; HER2+/- = human epidermal growth factor receptor 2 positive/negative; mDOR = median duration of response; mDOT = median duration of treatment; mOS = median overall survival; mPFS = median progression-free survival; mTTP = median time to progression; N = number of participants in the analysis population; NA = not available; NCCN = National Comprehensive Cancer Network; NR = not reached; NSCLC = non-small cell lung cancer; TC = thyroid cancer; USPI = United States Prescribing Information.

b A pooled analysis of the bevacizumab- versus placebo-containing arms (FOLFOX-4 and bevacizumab plus CAPEOX and bevacizumab vs FOLFOX-4 and placebo plus XELOX plus placebo) comprised the main analysis. Overall, 699 patients comprised the bevacizumab-containing arms and 701 comprised the placebo-containing arms.

c Xanthogranuloma is a subtype of histiocytosis. There are no NCCN recommended standard-of-care therapies available for xanthogranuloma. If systemic therapy is needed, methotrexate + cytarabine are suggested for use according to NCCN Histiocytosis guidelines.

d All studies related to brain describe recurrent disease post-radiation therapy (with or without chemo).

Source : Module 2.5 Clinical Overview Table 2.5.1.1

The FDA's Assessment:

FDA agrees with the Applicant's position that the prognosis for patients with advanced *RET* fusion-positive solid tumors is generally poor and treatment options beyond the first line as specified by NCCN guidelines vary by tumor type. When available, most second line and greater therapies are chemotherapy-based with overall responses rates of < 30%.

Table 2.2 includes available therapies in the second line or greater for the 14 tumor types included in the primary efficacy population (n=41).

Table 2-2: FDA Summary of Selected Available Therapies in Second Line or Greater for Tumor Types included in LIBRETTO-001

Tumor Type*	N	Available Therapies	ORR (95% CI)
Pancreatic	11	2L: 5-FU + nanoliposomal irinotecan post-gemcitabine	16% (9, 22)
		2L: Gemcitabine + nab-paclitaxel post-FOLFIRINOX	13% (5, 30)
Colorectal	10	2L: Irinotecan	15% (10, 20)
		2L: FOLFIRI +/- BEV	6% (0, 13)
		2L: 5-FU + Oxaliplatin	9% (4, 14)
		≥3L: Regorafenib	1% (0, 2)
		≥3L: Trifluridine + tipiracil	2% (0, 3)
		≥3L, RAS wildtype: panitumumab	22% (18, 26)
		≥3L, RAS wildtype: cetuximab	19% (16, 23)
Salivary	4	No standard of care available after 1L	
Unknown primary	3	No standard of care available after 1L	
Breast (HER2 negative)	2	2L: Paclitaxel	22% (15, 28)
		2L: Doxorubicin	31-38%
		2L: Capecitabine + docetaxel	32% (26, 38)
		≥3L: Vinorelbine	25% (13, 41)
Soft tissue sarcoma	2	2L: Pazopanib	4% (2, 8)
Xanthogranuloma	1	No standard of care available after 1L	
Carcinoid (bronchial)	1	No standard of care available after 1L	
Ovarian	1	2L: Platinum doublet chemotherapy ± BEV	19 – 53%
		≥3L: PARP inhibitor	Not reported
Small Intestine	1	2L: FOLFOX or FOLFIRI or CAPEOX +/- BEV	12-30%
Cholangiocarcinoma	1	2L: FOLFOX	Not reported
		2L: FOLFIRI	0%

Pulmonary carcinosarcoma	1	No standard of care available after 1L	
Rectal neuroendocrine	1	2L: Everolimus 2L: Lutetium 177 dotatate	2% (0, 5) 17% (13, 21)
Squamous cell skin cancer	1	2L: cemiplimab	46% (37, 55)

FOLFOX = 5-FU + oxaliplatin; FOLFIRI = 5-FU + irinotecan; FOLFIRINOX = 5-FU + oxaliplatin + irinotecan

3 Regulatory Background

U.S. Regulatory Actions and Marketing History

Table 3.1 outlines key U.S. Regulatory Actions and Marketing History.

Table 3-1. Summary of Regulatory Interactions

Date	Regulatory Interaction
31 Mar 2017	IND 133193 (including the protocol for LIBRETTO-001) was submitted to the Division of Oncology Products for the evaluation of selpercatinib in patients with solid tumors.
30 Aug 2018	FDA granted Breakthrough Therapy Designation to selpercatinib for the treatment of 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.
31 Aug 2018	FDA granted Breakthrough Therapy Designation to selpercatinib 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.
11 Oct 2018	FDA granted Breakthrough Therapy Designation to selpercatinib for the treatment of patients with advanced *RET* fusion-positive thyroid cancer who require systemic therapy, have progressed following prior treatment and have no acceptable alternative treatment options.
04 Dec 2019	NDA 213246 submitted to FDA for review.
08 May 2020	FDA granted accelerated approval for RETEVMO in patients with *RET* fusion-positive NSCLC, *RET* fusion-positive TC, and *RET*-mutant MTC.

Abbreviations: AACR = American Association for Cancer Research; BTD = breakthrough therapy designation; IND = investigative new drug; MTC = medullary thyroid cancer; NDA = New Drug Application; NSCLC = non-small cell lung cancer; *RET* = rearranged during transfection; sNDA = supplemental NDA; TC = thyroid cancer.

The FDA's Assessment:

FDA agrees with the Applicant's position. In addition, on May 19, 2022, Lilly was granted Orphan Drug Designation for tissue-agnostic *RET* fusion-positive solid tumors. This supplemental NDA was submitted on May 31, 2022 and was granted Priority Review.

Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Table 3.2 outlines the relevant presubmission and submission interactions with the FDA for RETEVMO for the *RET* fusion-positive tissue-agnostic indication.

Table 3-2. Summary of Presubmission and Submission Regulatory Activity

Date	Regulatory Interaction
6 May 2020	In response to an FDA Clinical Information Request related to the initial NDA for selpercatinib inquiring about plans to seek a tissue-agnostic indication, the sponsor submitted preliminary data from 26 patients with tumor types other than NSCLC or TC treated in LIBRETTO-001, and stated that the sponsor planned to approach the Agency to discuss whether there may be a path for a tissue-agnostic indication.
15 Dec 2020	Type C meeting to seek FDA input and agreement on a clinical data package to support a possible tissue-agnostic indication for selpercatinib for *RET* fusion-positive solid tumors. FDA provided feedback on expectations and considerations for an sNDA and suggested that sponsor request another meeting when additional data to support durable, objective responses across tumor types became available.
16 Jun 2021	Sponsor submitted a preliminary BTD request on 04 June 2021. At the 16 June 2021 teleconference, FDA stated that the data presented were unlikely to meet breakthrough criteria. For a tissue-agnostic sNDA, FDA indicated that they would consider the totality of selpercatinib *RET* fusion data.
30 Jul 2021	Type C guidance meeting to review the tissue-agnostic data presented at AACR, and to obtain agreement that a data package consistent with the AACR data would support filing of the sNDA.
10 Sep 2021	Request submitted to OOPD for a tissue-agnostic Orphan Drug Designation for selpercatinib for the treatment of patients with *RET* fusion-positive solid tumors.
30 Nov 2021	OOPD provided comments on the request for orphan drug designation for selpercatinib for the treatment of patients with *RET* fusion-positive solid tumors.
21 Dec 2021	Meeting package submitted to FDA for a 31 January 2022 Type B pre-sNDA meeting to discuss proposed tissue-agnostic supplement NDA.
15 Jan 2022	FDA issued an agreed iPSP for selpercatinib for the proposed tissue-agnostic indication

Date	Regulatory Interaction
25 Jan 2022	FDA preliminary comments received for Type B meeting. Sponsor did not require further discussion; the meeting was subsequently cancelled. FDA comments are addressed in Module 1: Annotated Meeting Minutes which provide the location of the information needed to address each of the points raised by the FDA.
19 May 2022	FDA granted Orphan Drug Designation to selpercatinib for the treatment of patients with tissue-agnostic *RET* fusion-positive solid tumors

Abbreviations: AACR = American Association for Cancer Research; BTD = breakthrough therapy designation; IND = investigative new drug; MTC = medullary thyroid cancer; NDA = New Drug Application; NSCLC = non-small cell lung cancer; *RET* = rearranged during transfection; sNDA = supplemental NDA; TC = thyroid cancer

The FDA's Assessment:

FDA agrees with the Applicant's position. This supplemental NDA was submitted on May 31, 2022 and was granted Priority Review.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

Office of Scientific Investigations (OSI)

OSI was not consulted for this sNDA. It was determined that inspections of investigational sites or the independent vendor for review of radiographic assessments were not needed as part of the review for this supplemental application. The clinical trial that forms the basis of this sNDA is the same study which supported the original approval of selpercatinib. Inspections were performed at the time of the original approval and there were no significant concerns. Refer to the original multidisciplinary review dated May 8, 2020 for a summary of inspection findings for the original NDA.

Product Quality

No additional product quality data were submitted in the supplemental application.

Clinical Microbiology

No clinical microbiology data were submitted in the supplemental application.

Devices and Companion Diagnostic Issues

No device or companion diagnostic data were submitted in the supplemental application. However, a PMC will be issued with the accelerated approval as follows:

> Commitment to support the availability of an in vitro diagnostic device that demonstrates the device is essential to the safe and effective use of selpercatinib for treatment of patients with *RET* fusion-positive solid tumors through an appropriate analytical and clinical validation study using clinical trial data.
>
> Study Completion: 09/2023
> Final Report Submission: 03/2024

5 Nonclinical Pharmacology/Toxicology

Executive Summary

No new nonclinical pharmacology or toxicology data were submitted in the supplemental application. Refer to the original multidisciplinary review dated May 8, 2020 for a summary of the nonclinical pharmacology/toxicology data for selpercatinib.

Referenced NDAs, BLAs, DMFs

The Applicant's Position:
Toxicology studies were previously submitted to FDA in support of the marketing application for the metastatic RET fusion positive non-small-cell-lung cancer (NSCLC) indication. The same studies support the tissue-agnostic RET fusion positive solid tumor indication.

Pharmacology

No new information is provided in the current submission.

The FDA's Assessment:
Not applicable

ADME/PK

No new information is provided in the current submission.

The FDA's Assessment:
Not applicable

Toxicology

No new information is provided in the current submission.

The FDA's Assessment:
Not applicable

6 Clinical Pharmacology

Executive Summary

The FDA's Assessment:

Selpercatinib received accelerated approval on May 8, 2020, for 3 indications:

1. The treatment of adult patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC)
2. The treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy
3. The treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)

NDA 213246 S-008 includes updated data from Study LIBRETTO-001 for a newly proposed tissue agnostic indication of selpercatinib for the treatment of adult patients with advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options. The proposed dosage regimen is the same as the currently approved body weight-based dosage for all 3 existing indications: 120 mg twice daily (BID) for patients with body weight <50 kg and 160 mg BID for patients with body weight ≥50 kg. Clinical Pharmacology information includes an updated selpercatinib population pharmacokinetics (PopPK) and exposure-response (E-R) report (data cut-off 15 Jun 2021). The PopPK and E-R for safety results were consistent with previous submissions. E-R for efficacy was inconclusive in the subset of patients with tissue agnostic *RET* fusion-positive solid tumors due to the small number of patients (n=37).

Exploratory analyses suggest that the genomic profile may have an impact on response to selpercatinib. However, the exploratory nature of the analyses and relatively low number of patients with each tumor type preclude definitive conclusions from the genomic profiling data collected in this trial.

Overall, the proposed dosage of 120 mg BID for patients with body weight <50 kg and 160 mg BID for patients with body weight >50 kg is acceptable in patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.

Recommendations: The Office of Clinical Pharmacology has reviewed the information contained in NDA 213246 S-008. The supplement is approvable from a clinical pharmacology perspective.

Summary of Clinical Pharmacology Assessment

Pharmacology and Clinical Pharmacokinetics

Data:

An overview of Selpercatinib PK Data was reported in previous submissions. Additional summaries related to the proposed indication are listed here:

- The steady-state PK parameters (Cycle 1 Day 8) overlapped considerably for all tumor types (MTC, NSCLC, and tissue-agnostic solid tumors) in patients dosed at 160mg BID.

  Steady-state PK data (Cycle 1 Day 8) following 160 mg BID administration for one patient with tissue-agnostic solid tumor enrolled after 15 June 2021 is similar to the PK data of patients with tissue-agnostic solid tumors reported previously. Note, there were two patients with tissue-agnostic solid tumors enrolled after 15 June 2021 (b) (6) (b) (6) but only one had PK samples. No new or unexpected AEs or safety risks were observed in these 2 patients.

The steady-state exposure of selpercatinib for patients taking 160 mg selpercatinib BID for different tumor types (MTC, NSCLC, and tissue-agnostic solid tumors) were compared using the Cycle 1 Day 8 AUC_{0-24} and C_{max} parameters obtained by non-compartmental analysis (NCA) (data cutoff date 10 June 2021) (Table 6.1). In this data cut, AUC_{0-24} and C_{max} PK parameters were calculated for 31 and 34 patients of the 43 patients in the tissue-agnostic populations, respectively, with evaluable PK data for NCA.

The steady-state PK parameters overlapped considerably for all tumor types. The higher geometric mean AUC_{0-24} values for NSCLC compared with MTC and tissue-agnostic populations reflect the high proportion of Asian patients contributing PK data for the NSCLC population. Asian patients were estimated to have 18.4% higher bioavailability compared with the non-Asian patients. Excluding the Asian patients from the comparisons, results in comparable C_{max} and AUC_{0-24} geometric means for all tumor types.

Table 6-1. Steady-State (Cycle 1 Day 8) Pharmacokinetic Parameters of Selpercatinib in Patients with Cancer

	MTC		NSCLC (Including Asian Patients)		NSCLC (Excluding Asian Patients)		Tissue-Agnostic	
	C_{max} (ng/mL)	AUC_{0-24} (h*ng/mL)	C_{max} (ng/mL)	AUC_{0-24} (h*ng/mL)	C_{max} (ng/mL)	AUC_{0-24} (h*ng/mL)	C_{max} (ng/mL)	AUC_{0-24} (h*ng/mL)
N	278	275	291	283	156	149	34	31

	MTC		NSCLC (Including Asian Patients)		NSCLC (Excluding Asian Patients)		Tissue-Agnostic	
	C_{max} (ng/mL)	AUC_{0-24} (h*ng/mL)	C_{max} (ng/mL)	AUC_{0-24} (h*ng/mL)	C_{max} (ng/mL)	AUC_{0-24} (h*ng/mL)	C_{max} (ng/mL)	AUC_{0-24} (h*ng/mL)
GM	2760	46600	3400	60200	2960	50700	2710	44300
GCV%	53	55	48	52	48	53	53	57
95%CI	1317, 5349	22581, 97778	1575, 6565	26816, 123975	1435, 5203	22159, 95188	1133, 5243	19076, 100589

Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours; CI = confidence interval; C_{max} = maximum plasma concentration; GCV% = geometric CV%; GM = geometric mean; MTC = medullary thyroid cancer; N = number of samples; NSCLC = non-small cell lung cancer.
Sources: Data available from 09 May 2017 to 10 June 2021. Module 2.5 Clinical Overview Table 2.5.3.1

The human population PK model for selpercatinib developed for the NSCLC sNDA was updated using pooled PK data from the LIBRETTO-001 study (data cut-off date 15 June 2021) and China study J2G-GH-JZJK (data available up to 12 April 2021), tested tumor type as a covariate, and re-estimated previously identified covariate effects.

- The PPK parameters changed 8% or less compared to report ELIL-PMX-SELPERCATINIB-3348.
- Tumor type was not found to be a significant covariate to any of the tested PK parameters.
- There was a 18.4% (bootstrap 95%CI: 11.3%, 25.9%) increase in bioavailability for Asian subjects in addition to effects of dose on CL/F and allometric body weight scaling.

Simulation from the population PK model suggests

- Steady-state AUC and C_{max} overlap considerably across all 3 tumor types (i.e., NSCLC, MTC, and tissue-agnostic solid tumors) as well as race (i.e., Japanese, Chinese, Asian, and non-Asian).
- A weight-based dosing (120 mg BID for subjects <50 kg and 160 mg BID for subjects ≥50 kg) was likely to produce similar exposures for subjects below or above 50 kg of weight.

The data above is provided in Module 2.5 Clinical overview Section 2.5.3.1.1 and 2.5.3.1.2.1.

The Applicant's Position:

The steady-state pharmacokinetics in the patients with *RET* fusion-positive tissue-agnostic solid tumors is consistent with the known pharmacokinetics of selpercatinib. The clinical pharmacology profile of selpercatinib is considered supportive of the dose regimen of 120 mg BID in patients below 50 kg and 160 mg BID in patients who are at least above 12 years of age.

The FDA's Assessment:
FDA agrees with the Applicant's position. The pharmacology and clinical pharmacokinetics of selpercatinib has been adequately characterized in patients with *RET*-fusion positive solid tumors. Refer to **Section 19.4 – OCP Appendices** for additional details.

General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

A weight-based dosing regimen of selpercatinib (120 mg for patients less than 50 kg, and 160 mg for those 50 kg or greater) has been approved by FDA for metastatic RET fusion-positive NSCLC, advanced or metastatic RET mutant MTC, and advanced or metastatic RET fusion positive TC.

Additional information related to the proposed indication is summarized here:

The steady-state pharmacokinetics in the patients with RET fusion-positive tissue-agnostic solid tumors is consistent with the known pharmacokinetics of selpercatinib. The steady-state PK parameters (Cycle 1 Day 8) overlapped considerably for all tumor types (MTC, NSCLC, and tissue-agnostic solid tumors) in patients dosed at 160mg BID. Tumor type was not found to be a significant covariate to any of the tested PK parameters.

A weight-based dosing (120 mg BID for subjects <50 kg and 160 mg BID for subjects ≥50 kg) was likely to produce similar exposures for subjects below or above 50 kg of weight.

The efficacy exposure-response analysis examined the ORR in patients with tissue-agnostic solid tumors from the LIBRETTO-001 study (15 June 2021 cut-off date). A subject with a partial response or a complete response was labeled as a responder. No statistically significant predictor ($p < 0.05$) was identified in patients with tissue-agnostic solid tumors. Given the small sample size of the analysis (n=37), the results should be interpreted with caution.

- The safety exposure-response analysis was conducted using all available data from the LIBRETTO-001 study (15 June 2021 cut-off date) for the AEs of interest (increases in ALT, increases in AST, hypertension, and hypersensitivity) for all patients, and for patients with tissue-agnostic solid tumor only. Possible predictors included selpercatinib steady-state AUC_{0-24}, dose reduction status, age, body weight, and sex. It was found that

  The safety exposure-response analysis results for the 4 AEs of interest with all data appeared to be similar to those previously reported for all patients. None of the AEs of interest listed above showed an increased risk with increases in selpercatinib exposure for all patients. In the overall population, subjects with a dose reduction had higher risk of all AEs. However, this may be due to the dose reductions when AEs occurred. Steady-

state AUC_{0-24} was the predictor for ALT, AST, and hypertension AEs. For the AE of hypertension, compared to the reference age of 58 years, the risk of the AE is higher in subjects older than 58 years, whereas the risk was lower in subjects younger than 58 years.
For patients with tissue-agnostic solid tumors, no statistically significant predictor was identified for increases in ALT and increases in AST. Only age was identified as a predictor of AE for hypertension. No hypersensitivity AE were recorded in this subpopulation. Given the small sample size of the analysis (n=37), the results should be interpreted with caution.

The data above is provided in Module 2.5 Clinical overview Sections 2.5.3.1.1, 2.5.3.1.2.1, 2.5.3.1.2.2, and 2.5.3.1.2.3.

The Applicant's Position:

In this subgroup of patients, the exposure-response analyses for efficacy or for AEs of interest did not identify any treatment-related predictors. Overall, the totality of data from LIBRETTO-001 demonstrates a favorable benefit-risk profile.
For the tissue agnostic indication, Sponsor recommends using the same weight-based dose regimen as NSCLC and TC, i.e. 120 mg BID (in patients <50 kg) and 160 mg BID (in patients ≥50 kg).

The FDA's Assessment:
FDA agrees with the Applicant's position. Results of E-R analyses for safety were similar to those observed in previous submissions (Refer to the Original NDA 213246 Multidisciplinary Review). Refer to **Section 19.4.2 – Exposure-Response Analysis** for additional details on the updated analyses.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

No new recommendation compared to previous submissions.

The FDA's Assessment:
FDA agrees that there are no new recommendations for therapeutic individualization. The recommended dosage of selpercatinib for all approved indications is based on body weight (120 mg BID for patients with body weight <50 kg and 160 mg BID for patients with body weight ≥50 kg). Refer to the Original NDA 213246 Multidisciplinary Review and Clinical Pharmacology reviews for final reports of PMR 3829-7 (hepatic impairment) and PMR 3829-8 (renal impairment) for intrinsic factor assessments.

6.2.2.3. Outstanding Issues

The Applicant's Position:
None

The FDA's Assessment:
A new clinical pharmacology PMR (to evaluate effects of selpercatinib on a BCRP substrate) was issued under NDA 213246 S-007. Language requesting additional genomic profiling data in order to investigate the effects of genomic alterations on response to selpercatinib is included in the Post-Marketing Requirement (PMR) for a confirmatory trial. There are no other outstanding clinical pharmacology issues in the current supplement.

Comprehensive Clinical Pharmacology Review

General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

No new recommendations compared to previous submissions.

The FDA's Assessment:
The clinical pharmacology of selpercatinib has previously been described in detail in the clinical pharmacology review of the original NDA 213246 submission. Refer to the Original NDA 213246 Multidisciplinary Review for a detailed description of the clinical pharmacology data.

Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:
The efficacy exposure-response analysis examined the ORR in patients with tissue-agnostic solid tumors from the LIBRETTO-001 study (15 June 2021 cut-off date). A subject with a partial response or a complete response was labeled as a responder. No statistically significant predictor ($p < 0.05$) was identified in patients with tissue-agnostic solid tumors. Given the small sample size of the analysis (n=37), the results should be interpreted with caution.
These data are provided in Module 2.5 Clinical overview Section 2.5.3.1.2.2.

The Applicant's Position:
Although no clear exposure-response relationship was established for patients with tissue-agnostic solid tumors, considering the small sample size, majority patients on 160 mg BID, similarity of PK across tumor types, and that the ORR for the this subpopulation included in this exposure-response analysis was 43.2% (16 responders of 37 subjects) (ELIL-PMX-SELPERCATINIB-3499), the sponsor considers the data supportive of selpercatinib's efficacy in this population based on the totality of data, and the overall benefit-risk profile and effect observed from LIBRETTO-001.

The FDA's Assessment:
FDA agrees with the Applicant's position. The primary evidence of effectiveness is the ORR of 44% in patients with *RET* fusion-positive solid tumors (other than NSCLC and thyroid cancer). Refer to **Section 8.1.2 – Study Results**.

Genomic Profiling

The Applicant submitted genomic profiling data for patients included in the tissue agnostic portion of LIBRETTO-001. These data included information about RET fusion partners, tumor mutational burden (TMB), microsatellite instability (MSI) status, and co-occuring mutations. Data were collected from individual sites and multiple platforms (N=13) were utilized to generate the genomic profile data, with most platforms utilizing NGS and only 1 platform utilizing FISH. The most common platforms utilized for genomic profiling in the 41 efficacy evaluable patients were the FoundationOne platform (N=23; 56%), the Guardant 360 platform (N=4; 10%), and the Archer FusionPlex platform (N=3; 7%). Exploratory analyses were conducted to assess the potential impact of these molecular alterations on selpercatinib response. MSI-High status was only detected in a single patient with colon cancer, precluding analyses in regards to the impact of MSI status on ORR.

Of the 41 efficacy evaluable patients, 39 patients had RET gene fusions with 15 unique RET fusion partners identified and 2 patients had RET gene rearrangements. Identified gene fusion partners included NCOA4, CCDC6, KIF5B, ETV6, CGNL1, ERC1, GOLGA5, GPHN, KIAA1217, PRKAR1A, RASAL2, SPECC1L, TAF3, TFG, TRIM24, AND TRIM33. The most common RET fusion partners were NCOA4 (N=16), CCDC6 (N=6), and KIF5B (N=4). As compared to the ORR of 44% in the tissue agnostic portion of the trial, response rates were numerically higher in patients with the CCDC6 fusion partner (ORR=67%) and numerically lower in patients with the NCOA4 (ORR=31%) and KIF5B (ORR=25%) fusion partners. Among the 16 patients of any tumor type with NCOA4 as the fusion partner, 9 had colon cancer and among the 10 patients with colon cancer, 9 had NCOA4 as the fusion partner.

TMB-High (≥10mut/MB), TMB-Intermediate (5mut/MB < x <10mut/MB), and TMB-Low (≤5mut/MB) status were available for 26 of the 41 patients and numerical estimates of TMB were available for 25 of the 41 patients. Exploratory analyses showed that patients with TMB-Low status had an ORR of 61% versus 25% in patients with either TMB-High or TMB-Intermediate status. Non-responders had slightly elevated TMB (mean=4.9mut/MB) versus responders (mean=3.4mut/MB). Mean TMB values were also elevated in colon cancer (8mut/MB) versus pancreatic (3.9mut/MB), salivary (3.3mut/MB), or patients with tumor types other than colon (2.9mut/MB).

Co-occurring gene mutation data showed that 30 of the 41 patients had at least one gene mutation, overexpression, or amplification identified. The most commonly identified co-occurring gene mutations were TP53 (32%), CDKN2A/2B (20%), and SMAD4 (15%). Exploratory analyses showed that patients with mutations in TP53 had lower ORR (23%) versus those with wildtype TP53 (54%). While TP53 was the most commonly mutated gene overall, a larger percentage of patients had TP53 mutations in colon cancer (70%) than in pancreatic (18%) and salivary (25%), the next most prevalent tumor types.

In summary, exploratory analyses investigating the impact of genomic profile on ORR suggest that RET fusion partner (specifically the presence of NCOA4), TP53 mutation status, and TMB may each have an impact on response to selpercatinib. In addition, the presence of NCOA4 as a RET fusion partner and TP53 mutations were both enriched in patients with colon cancer within this trial. It should be noted that the ORR was lower in patients with colon cancer than in patients with other tumor types such as lung, pancreatic, or thyroid. However, the exploratory nature of the analyses, the relatively low number of patients with each tumor type, and the complexities of combining data across several different molecular platforms preclude definitive conclusions from the genomic profiling data collected in this trial. Language requesting additional genomic profiling data in order to investigate the effects of genomic alterations on response to selpercatinib is included in the PMR for a confirmatory trial.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:
The steady-state pharmacokinetics in the patients with *RET* fusion-positive tissue-agnostic solid tumors is consistent with the known pharmacokinetics of selpercatinib (Section 6.2.2.1).

In this subgroup of patients, the exposure-response analyses for efficacy or for AEs of interest did not identify any treatment-related predictors (Section 6.2.2.1).

The Applicant's Position:
The sponsor considers the proposed weight-based dose regimen (120 mg BID in patients below 50 kg and 160 mg BID in patients who are at least 50 kg) to be appropriate for patients with tissue-agnostic solid tumors.

The FDA's Assessment:
FDA agrees with the Applicant's position. Refer to the Original NDA 213246 Multidisciplinary Review for discussion of the recommended selpercatinib dosage in other approved indications. Given the similarity in PK between tumor types and the lack of significant E-R relationships for efficacy or safety in the new tissue agnostic patient population, use of the same recommended dosage (120 mg BID for patients with body weight <50 kg and 160 mg BID for patients with body weight ≥50 kg) is acceptable.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The Applicant's Position:

No new recommendation compared to previous submissions.

The FDA's Assessment:
FDA agrees with the Applicant's position. Refer to the Original NDA 213246 Multidisciplinary Review and Clinical Pharmacology reviews for final reports of PMR 3829-7 (hepatic impairment) and PMR 3829-8 (renal impairment) for intrinsic factor assessments.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:
There are no new data on selpercatinib food-drug interactions.

There are no new data on selpercatinib DDIs with OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE-1 and MATE-2 transporters (serum creatinine), or Cytochrome P450 enzymes. A study to explore the interaction of selpercatinib with P-gp substrate has been submitted in NSCLC sNDA 2021 sequence 0586.

The Applicant's Position:

No new recommendation compared to previous submissions.

The FDA's Assessment:

FDA agrees with the Applicant's position. Refer to the clinical pharmacology review for NDA 213246 S-007 for assessment of the P-gp substrate drug interaction study and the Original NDA 213246 Multidisciplinary Review for other drug interaction information.

X	X
Primary Reviewers Lauren Price, PharmD Yangbing Li, PhD Jeffrey Kraft, PhD	Team Leaders Jeanne Fourie Zirkelbach, PhD Youwei Bi, PhD Sarah Dorff, PhD

7 Sources of Clinical Data

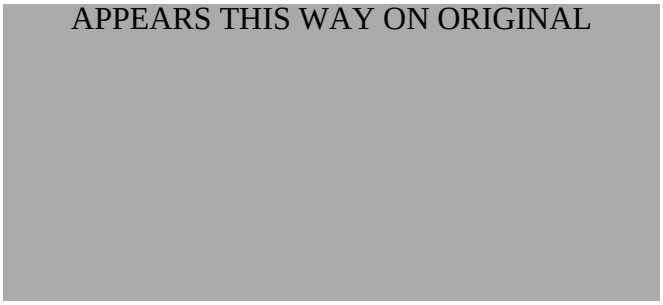


Table of Clinical Studies

Data:
A brief overview of LIBRETTO-001 is provided in Table 7.1.

Table 7-1 Clinical study Pertinent to the claimed Indication

Study Identifier; Study Status; Participating Countries	Objectives Endpoints	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Patients and Diagnosis of Patients	Study Initiations Date and Data Cutoff Date
LOXO-RET-17001 (J2G-OX-JZJA) A Phase 1/2 Study of Oral LOXO-292 in Patients with Advanced Solid Tumors, Including *RET* Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors with RET Activation (LIBRETTO-001) Status: Ongoing Participating TA countries: • United States • Japan • Israel • Switzerland • Denmark • France • Singapore	**Primary**: ORR based on RECIST 1.1 or RANO, as appropriate to tumor type, as assessed by IRC. **Secondary:** ORR based on Investigator assessment using RECIST 1.1, TTR, TTBR, DOR, CBR, and PFS based on IRC and Investigator assessment, and OS	Phase 1/2, multicenter, multi-cohort, open-label study, does-escalation, Dose-expansion	The recommended Phase 2 dose of selpercatinib (160 mg BID) was selected in Phase 1 and has been used as the starting dose for patients in the Phase 2 dose-expansion phase of the study (currently ongoing)	45 participants in the Tissue-Agnostic safety analysis • adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) • adult and pediatric patients ≥12 years of age with advanced or metastatic RET mutant MTC who require systemic therapy, and • adult and pediatric patients ≥12 years of age with advanced or metastatic RET fusion positive thyroid cancer (TC) who require systemic therapy	*Study Initiation: 09 May 2017 (First participant* visit *Database lock for the interim CSR report:* 24 Sept 2021

Study Identifier; Study Status; Participating Countries	Objectives Endpoints	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Patients and Diagnosis of Patients	Study Initiations Date and Data Cutoff Date
				and who are radioactive iodine refractory (if radioactive iodine is appropriate).	

Source: Module 2.5 Clinical overview; Module 2.7.3 Summary of clinical Efficacy; Tissue-Agnostic Interim CSR Synopsis

The Applicant's Position:

The primary study supporting the evaluation of efficacy in this sNDA is LIBRETTO-001. A detailed description of the results is provided in the sections below.

The FDA's Assessment:

FDA agrees with the Applicant's position. FDA reviewed a single clinical trial, LOXO-RET-17001 (LIBRETTO-001), as the source of clinical data for the supplemental application. Data from LIBRETTO-001 was used to support the original approval of selpercatinib.

8 Statistical and Clinical Evaluation

Review of Relevant Individual Trials Used to Support Efficacy

A Phase 1/2 Study of Oral LOXO-292 in Patients with Advanced Solid Tumors, Including *RET* Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors with RET Activation (LIBRETTO-001)

Trial Design

The Applicant's Description:

LIBRETTO-001 is a Phase 1/2, single-arm, multi-cohort, multi-country, open-label, dose-escalation/dose-expansion trial in patients 12 years or older with advanced solid tumors, including RET fusion-positive solid tumors, RET-mutant MTC, and other tumors with RET activation. The Phase 1 portion is completed. The Phase 2 portion is ongoing and uses the RP2D dose of 160 mg BID selpercatinib.

The single-arm study design was chosen because, at the time of trial initiation, no approved selective targeted therapy was available. The lack of an active comparator for testing the relative efficacy and safety of selpercatinib is a limitation of this design, but the rarity of the patient population limited the feasibility of conducting a randomised trial against standard regimens early in development. To establish the robustness of the selpercatinib efficacy, the consistency of outcomes was evaluated across indications and multiple pre-defined and other supportive analysis sets, and between the investigator and IRC efficacy assessments.

Patients from the Phase 1 and Phase 2 portions of LIBRETTO-001 were included in analysis sets evaluating efficacy in specific tumor types. In addition to patients previously included in the original NDA (i.e., patients with advanced or metastatic RET-fusion NSCLC and TC, as well as RET-mutant MTC), patients with RET fusion-positive solid tumors other than NSCLC or TC were enrolled per protocol if they had progressed on or were intolerant to standard-of-care therapies, or if they met 1 of the following criteria:

no standard therapy existed,
the patient declined standard therapy, or
in the opinion of the investigator, the patient was not a candidate for, or would be unlikely to tolerate or derive clinical benefit from, standard therapy.

The primary efficacy analysis set presented in this submission consists of patients enrolled in LIBRETTO-001 with RET fusion-positive solid tumors other than NSCLC or TC. This analysis set is defined as the **Tissue-Agnostic Efficacy Population**.

The **Tissue-Agnostic Efficacy Population** included all patients with RET fusion-positive tissue-agnostic solid tumors which met the following criteria:

achieved at least 6 months of potential follow-up from the first dose as of 24 September 2021, and
all responders (based on Investigator assessment) were followed for at least 6 months from the onset of response unless they progressed or died earlier, or discontinued earlier due to other reasons.

The FDA's Assessment:
FDA generally agrees with the Applicant's description of the clinical trial design. FDA notes that the study population is heterogenous and allows for patients with various tumor types and prior lines of therapy. Efficacy may depend on many external factors including prior therapy, disease histology, and other prognostic factors; and whether consistent efficacy is expected across tumor types is difficult to determine given the heterogeneity mentioned above. The small sample size for each of the tumor types is a further limitation, and robustness of the treatment effect across tumor types is challenging to assess.

In the Phase 2 portion of LIBRETTO-001, patients were enrolled to one of seven cohorts. The majority of patients (n=35) included in the Tissue-Agnostic Efficacy Population were enrolled to Cohorts 1 and 5 from the Phase 2 portion of the study, which were opened for patients with advanced *RET* fusion positive solid tumors who progressed on or were intolerant to first line therapy or did not meet the criteria for the other *RET* fusion positive cohorts (i.e., had not progressed on first line therapy or were not treatment naive), respectively. One patient was enrolled in Cohort 2 of the Phase 2 portion of the study, for patients with advanced *RET* fusion positive solid tumors without standard first-line therapy. There were 5 patients included in the Tissue-Agnostic Efficacy Population from the Phase 1 portion of the study, including one patient who began dosing with selpercatinib at 80 mg BID before escalating to 160 mg BID and one patient who only received 120 mg BID.

Study Endpoints

The Applicant's Description:

Phase 2 primary and secondary endpoints
The primary objective of the Phase 2 portion is the antitumor activity of selpercatinib determined by ORR using RECIST 1.1 or RANO, as appropriate for tumor type, as assessed by IRC (Eisenhauer et al. 2009).

ORR by Investigator assessment, DOR, PFS, and OS were collected as secondary endpoints.

The FDA's Assessment:

FDA agrees with the Applicant's summary of study endpoints in LIBRETTO-001. ORR supported by DOR based on RECIST 1.1 or RANO, depending on tumor type, are reasonable endpoints to assess anti-tumor efficacy of selpercatinib in this non-randomized multi-cohort trial without a control arm for comparison. ORR as assessed by blinded independent review committee (BIRC) was the primary endpoint and defined as the proportion of patients with best overall response of a confirmed CR or PR. Response was confirmed by a repeat assessment after 28 or more days.

DOR was the key secondary endpoint. Other time-to-event endpoints such as PFS and OS are difficult to interpret in a non-randomized setting due to a lack of appropriate comparator arm.

Per the LIBRETTO-001 protocol, patient imaging studies were reviewed by a blinded independent review committee (BIRC). As described in the Imaging Review Charter, independent radiologists were blinded to investigator site and subject identifiers, imaging dates, local radiology assessments, and assessments made by other BIRC readers. Available clinical information was limited to subject number, primary tumor type, known areas of prior radiation therapy, caliper measurements of palpable lesions, on-study pathology, or cytology results.

Statistical Analysis Plan and Amendments

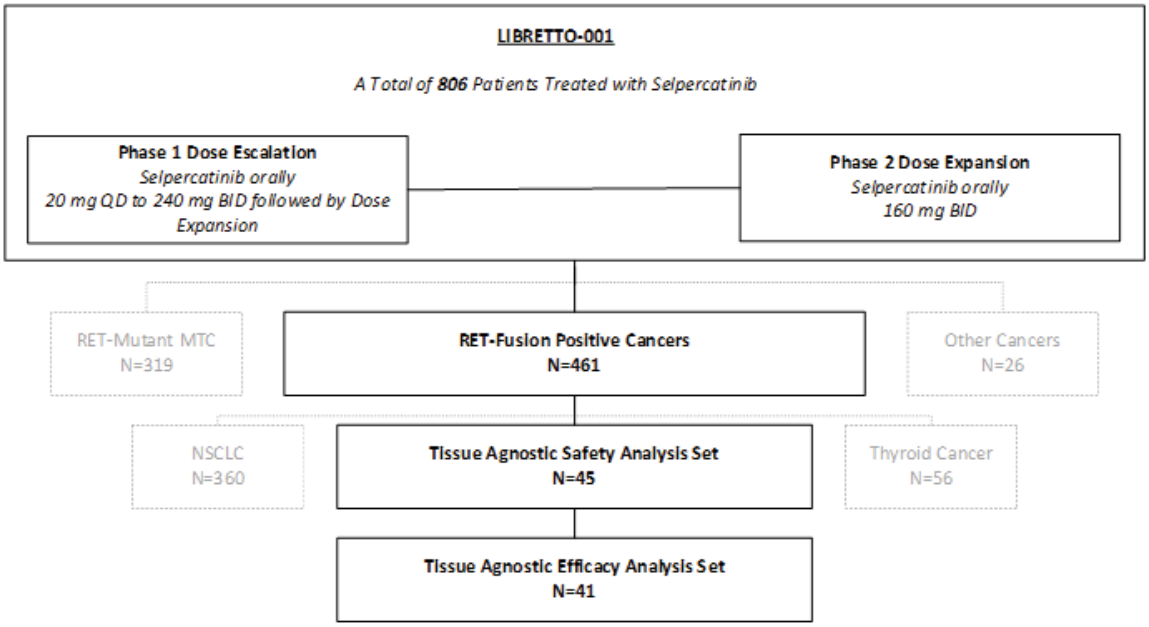
The Applicant's Description:

The protocol (Protocol and addenda) and the JZJA Tissue-Agnostic SAP Version 2.0 (Statistical methods) provide the planned analyses for the study, comparisons, statistical tests, and determination of sample size.
Patients enrolled into the Phase 1 dose escalation as well as the Phase 1 and Phase 2 dose-expansion cohorts were grouped to derive the analysis sets.
The goal of the arrangement of these various datasets was to

- maximize information through the consolidation of data from both Phase 1 and Phase 2 parts of LIBRETTO-001, and
- define groupings based on clinically meaningful distinctions, resulting in similarity of patients within a group, thus, facilitating the interpretation of results.

The interim Tissue-Agnostic CSR provides clarification regarding the derivation of the analysis sets that support evaluation of the tissue-agnostic data for selpercatinib.

Figure 8.1 Presents a flow diagram depicting the derivation of Tissue-Agnostic data analysis sets as of 24 September 2021.
As of the data cutoff date, 461 patients with *RET* fusion-positive cancer were enrolled, of which 45 patients had *RET* fusion-positive tissue-agnostic solid tumors. Of these 45 patients, 41 patients were considered eligible for efficacy analysis.



Abbreviations: BID = twice daily; MTC = medullary thyroid cancer; N = number of patients in the population; NSCLC = non-small cell lung cancers; *RET* = REarranged during Transfection; QD = once daily.
Note: Dashed lines indicate patients not included in any Tissue-Agnostic dataset.
Data cutoff date: 24 September 2021
Source: Mod 2.7.3 SCE Section 2.7.3.2.1.1

Figure 8-1. Flow diagram depicting Tissue-Agnostic data analysis sets LIBRETTO-001

The FDA's Assessment:

FDA agrees with the Applicant's summary of the statistical analysis plan. Statistical analysis plan version 2 was discussed in a pre-NDA meeting, including the derivation of the analysis set for efficacy. FDA advised the applicant to (1) provide a detailed description of the patients with IRC-assessed non-measurable disease, including tumor type, sites of disease and rationale for response determination to justify their inclusion in the efficacy population; and (2) provide a list of patients who met the criteria for the efficacy analysis set except did not have at least 6 months of follow-up from the first dose of selpercatinib including, the diagnosis, response data and the time since the first

dose.

Of 45 patients in the Tissue Agnostic Safety Analysis Set who had *RET* fusion-positive solid tumors other than NSCLC and thyroid cancer, 4 patients were considered not eligible for the efficacy analysis because they did not have at least 6 months of follow-up from the time of first dose as of the Data Cut-off of September 24, 2021. Three of the four patients excluded from the efficacy analysis set had measurable disease per investigator assessment.

The Applicant's Description:

The Sponsor implemented all changes in study conduct via 9 protocol amendments, labeled LOXO-RET-17001 Version 1 through LOXO-RET-17001 Version 9 (Table 8.1).

Table 8-1. LOXO-RET-17001 Protocol Amendments and Approval Dates

Trial Document	Approval Date	Important Modifications
Protocol LOXO-RET-17001 Version 1	01 Mar 2017	
Protocol LOXO-RET-17001 Version 2	27 Mar 2017	The following revisions were made based on FDA IND review: • The starting dose was updated to 20 mg QD. • The study design was updated from rolling six to 3+3 and dose escalation criteria changed.
Protocol LOXO-RET-17001 Version 3	20 Jul 2017	New strengths/formulations of selpercatinib were added. Risks were updated to include possible pancreas injury. Eligibility age for enrolment was lowered where allowed. Clarified that patients with progressive disease could be allowed to continue selpercatinib with Sponsor approval. Inclusion/Exclusion Criteria regarding required tissue samples, disease status, baseline labs, concomitant medications, and comorbidities were revised. Included additional guidelines for dose holds and modifications.
Protocol LOXO-RET-17001 Version 4	21 Nov 2017	Exclusion Criteria regarding timing of prior cancer therapies were revised.
Protocol LOXO-RET-17001 Version 5	30 May 2018	The primary purpose of this amendment was to update the trial design from a two-part Phase 1 (dose escalation and dose expansion) study to a Phase 1/Phase 2 study. In the ongoing Phase 1 (dose escalation) portion of the study, selpercatinib showed promising early evidence of durable anti-tumor activity in patients with RET-altered cancers. While the target patient population for this study

Trial Document	Approval Date	Important Modifications
		remained the same, the following substantive changes were made: RP2D of 160 mg BID was selected. Modifications were made to the composition of the cohorts in the Phase 2 (dose expansion) portion of the study and increase in sample size for each cohort with additional criteria by cohort based on disease status/prior treatments Additional objectives and endpoints were added to and relevant statistical analyses were updated. Clarifications were made to define activating *RET* mutations, eligibility for patients with renal insufficiency, PK sampling schedule, and imaging requirements.
Protocol LOXO-RET-17001 Version 6	11 Sept 2018	Added Dose Level 9 Dose 200 mg BID (total daily dose: 400 mg) Minor revision of Inclusion Criteria related to previous therapies and ongoing infections. Added time points for hepatic safety labs (AST, ALT, alkaline phosphatase) Added clarifications to prohibited concomitant medications and guidance for toxicity management.
Protocol LOXO-RET-17001 Version 7	18 Oct 2018	Increased the number of patients, sizes of cohorts (up to ~750 patients for Phase 2). Clarified the method and timing of reporting of AEs and SAEs. Revised Exclusion Criterion related to symptomatic CNS disease. Deleted the Per-Protocol Analysis Set and planned to use Safety Analysis Set as the alternative.
Protocol LOXO-RET-17001 Version 8	10 Jun 2019	Updated risk profile and new information in Investigator Brochure Increase total number of patients and add a cohort for patients previously treated with a RET inhibitor. Update dose modification guidance Eligibility criteria were added, removed, or modified (as detailed in protocol Section 3.3.1). Tests and evaluations were updated to add tests at additional time points and increase frequency of tests. Definition of life-threatening AEs was updated. Examples of multiple kinase inhibitors and RET activating mutations were updated.

Trial Document	Approval Date	Important Modifications
Protocol LOXO-RET-17001 Version 9	03 Jun 2020	Updated risk profile and new information in Investigator Brochure Increase total number of patients Update dose modification guidance Aligned changes added in response to EC/RA queries in PA8.1 (Denmark), PA8.3 (Germany), and PA8 addendum (Canada). Clinical safety and data updates were made to align with the IB V7.0. Reduced the requirement for in-clinic visits beyond C7 and provided the options of telemedicine and visits to local healthcare providers during nondisease assessment cycles.

None of the modifications to the protocol are considered to meaningfully impact the outcomes for patients in the Tissue-Agnostic efficacy population.

The FDA's Assessment:

FDA agrees with the Applicant's position. Between protocol versions 5 and 7, the sample size for Cohorts 1-5 was increased from up to 100 patients allowed in each cohort to up to 150 patients allowed in each cohort. This planned increase in sample size did not impact the tumor agnostic efficacy set substantially.

Major changes to the protocol made after the accelerated approval in May 2020 did not have an impact on the integrity of the trial or interpretation of the results.

Study Results

Compliance with Good Clinical Practices

Data:

This study was conducted in accordance with the protocol and:

- consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- applicable International Conference for Harmonisation Good Clinical Practice guidelines, and
- applicable laws and regulations.

The Applicant's Position:

LIBRETTO-001 was conducted in compliance with Good Clinical practice

The FDA's Assessment:
The Applicant's statement that Study LOXO-RET-17001 (LIBRETTO-001) was conducted in accordance with Good Clinical Practice (GCP) guidelines was reviewed in the CSR.

Financial Disclosure

Data:

Sponsor is submitting a financial disclosure certification document in Module 1.3.4. This documentation provides a listing of all principal investigators and sub-investigators who participated at sites that enrolled patients with RET fusion-positive tissue-agnostic solid tumors in the single study, LIBRETTO-001, included in the sNDA submission – indicating whether the investigators have provided a Certification (Form 3454) or a Disclosure statement (Form 3455). This listing represents any new or updated financial disclosure information provided for these investigators.

The Applicant's Position:

As this is a multi-site, multi-national study (the Tissue-Agnostic patients were enrolled across 30 sites in 8 countries) and the primary endpoint is assessed by a blinded, independent, review committee, the financial disclosure data should not impact the integrity of the data presented in this sNDA.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Patient Disposition

Data:

Of the 45 tissue-agnostic patients treated with selpercatinib in LIBRETTO-001 (Tissue-Agnostic Safety Population), 41 were efficacy eligible (Tissue-Agnostic Efficacy Population). Patient disposition for the Tissue-Agnostic Safety and Efficacy Populations is summarized in Table 8.2.

**Table 8-2. Patient Disposition
Tissue-Agnostic Efficacy Analysis Sets**

	***RET* Fusion-Positive Tissue-Agnostic Solid Tumors**
Study Disposition	**Efficacy Analysis Set N = 41 n (%)**
Treatment status	
Discontinued	23 (56.1)
On treatment	18 (43.9)
Reason for treatment discontinuation	
Disease progression	13 (31.7)
Adverse event	4 (9.8)
Withdrawal of consent	2 (4.9)
Death	2 (4.9)
Other	1 (2.4)
Lost to follow-up	1 (2.4)
Study status	
Discontinued	21 (51.2)
On study	20 (48.8)
Reason for study discontinuation	
Withdrawal of consent	2 (4.9)
Lost to follow-up	1 (2.4)
Death	18 (43.9)

Abbreviations: N = number of patients in analyses set; n = number of patients in the specific category; *RET* = Rearranged during Transfection.
Data cutoff date: 24 September 2021.
Source: Module 2.7.3 SCE Table 2.7.3.3

The Applicant's Position:

As of 24 September 2021, 18 (43.9%) of the 41 patients in the Tissue-Agnostic Efficacy Population were still on treatment. Disease progression (31.7%) was the most common reason for treatment discontinuation. The number of patients who discontinued treatment due to an TEAE was low (9.8%).

The FDA's Assessment:

FDA agrees with the Applicant's summary of patient disposition. A total of 41 patients were included in the Tissue-Agnostic Efficacy Population, with 44% continuing on treatment as of the data cut-off date. Of the 56% of patients who discontinued treatment, reasons for treatment discontinuation included disease progression (32%), adverse events (10%), withdrawal of consent (5%), death (5%), patient decision (2%) and loss to follow-up (2%).

Protocol Violations/Deviations

Data:

Important protocol deviations were defined as any deviation from the protocol which could potentially impact the study assessment, participant rights, and the study integrity. Important protocol deviations were identified prior to data cutoff and included CSR-reportable deviations that are summarized in Table 8.3**.**

Table 8-3. Summary of Important Protocol Deviations Tissue-Agnostic Safety Analysis Set

Category	***RET* Fusion-Positive Tissue-agnostic Solid Tumors (N=45) n (%)**
Patients with major protocol deviations	11 (24.4)
Investigational product	3 (6.7)
Study procedures	3 (6.7)
SAE reporting	2 (4.4)
Restricted concomitant medication change	2 (4.4)
Inclusion criteria	2 (4.4)
Withdrawal criteria	1 (2.2)

Abbreviations: N = number of patients; n = number of patients in the specific category; *RET* = Rearranged during Transfection; SAE = serious adverse event.
Date cutoff date: 24 September 2021
Source: Tissue-Agnostic Interim CSR Section 4, Table 4.2.

The Applicant's Position:

The protocol deviations that occurred were reviewed by the Sponsor and were considered unlikely to have affected the safety of the patients or the results or conclusions presented in this report.

The FDA's Assessment:

FDA agrees that important on-study protocol deviations as identified by the Applicant were primarily related to the investigational product (e.g., dosing diary not dispensed, dose level changed without sponsor approval) and study procedures (e.g., missing single labs or vital signs, prohibited concomitant medications). These deviations are unlikely to have a significant impact on study results.

Table of Demographic Characteristics

Data:

Patient demographics for the Tissue-Agnostic Efficacy Analysis Set as of 24 September 2021 are summarized in Table 8.4 .

Table 8-4. Summary of Demographics Tissue-Agnostic Safety and Efficacy Analysis Sets

	***RET* Fusion-Positive Tissue-Agnostic Solid Tumors N=41 n (%)**
Sex	
Female	22 (53.7)
Male	19 (46.3)
Age	
Median years (min-max)	50 (21-85)
Race	
White	28 (68.3)
Black or African American	2 (4.9)
Asian	10 (24.4)
Native Hawaiian or other Pacific Islander	1 (2.4)
Country	
United States	26 (63.4)
Japan	9 (22.0)
Israel	2 (4.9)
Switzerland	1 (2.4)
Denmark	1 (2.4)
France	1 (2.4)
Singapore	1 (2.4)
Ethnicity	
Hispanic or Latino	3 (7.3)
Not Hispanic or Latino	37 (90.2)
Missing	1 (2.4)
ECOG performance status	
0	14 (34.1)
1	25 (61.0)
2	2 (4.9)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; ax = maximum; min = minimum; N = number of patients; n = number of patients in the specific category; *RET* = REarranged during Transfection; SD = standard deviation.
Data cutoff date: 24 September 2021.
Source:Module 2.7.3 SCE Table 2.7.3.4

The Applicant's Position:

The sex of the population was well balanced with 54% of the participants female. Median age for the population was 50 years old (range: 21-85). A high proportion of patients were 18 to <45

years of age (36.6%). Median age in the Tissue-Agnostic Efficacy Population is younger than typically observed in cancer studies and is reflective of the general biology of cancers with driver alterations (Wang et al. 2012).
The majority of Tissue-Agnostic Efficacy Population were either white (68%) or Asian (24%) and black or African American participants made up 5% of the population. These numbers are generally reflective of the population demographics in the US (76% White, 13% Black, 6% Asian, 0.2% Hawaiian/Pacific Islander [US Census Estimates 2021]) with some over-representation in the Asian population and under-representation in the African America population. The majority of patients were enrolled in the US (63.4%).

The FDA's Assessment:
FDA agrees with the Applicant's presentation of demographic composition of the patients enrolled in the LIBRETTO-001 trial. In the Tissue-Agnostic Efficacy Analysis Set, the median age was 50 years (range 21 to 85), which is younger than the overall safety population (n=796; median age 59 years). Patients were evenly divided by sex. Most patients had a good performance status; ECOG was 0-1 in 95%.

Regarding race and ethnicity, 68% were White, 24% were Asian, and 4.9% were Black; 7% were Hispanic or Latino. These percentages are similar to the overall safety population. Notably, the number of patients in the Tissue-Agnostic Efficacy Analysis Set is small, and would not be representative of the entire population with a given tumor type. For most cancers, 5% Black or African American patients and 7% Hispanic patients are an under-representation, and 24% Asian patients is an over-representation for the US population. However, given the rarity of these cancers and the limited knowledge regarding the specific incidence of *RET* fusions by race and ethnicity, some population variability may be expected.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Baseline disease characteristics for the Tissue-Agnostic efficacy Analysis Set as of 24 September 2021 are summarized in Table 8.5.

The LIBRETTO-001 Tissue-Agnostic Efficacy dataset included 14 unique tumor types. The most common tumor types were pancreatic, colorectal, and salivary gland. The most common *RET* fusion partner was NCOA4 (39.0%).

Table 8-5. Summary of Baseline Disease Characteristic Tissue-Agnostic Efficacy Analysis Set

	***RET* Fusion-Positive Tissue-Agnostic Solid Tumors N=41 n (%)**
Primary diagnosis	
Pancreatic	11 (26.8)
Colon	10 (24.4)
Salivary[a]	4 (9.8)
Unknown primary	3 (7.3)
Sarcoma	2 (4.9)
Breast	2 (4.9)
Xanthogranuloma[c]	2 (4.9)
Carcinoid[d]	1 (2.4)
Rectal neuroendocrine	1 (2.4)
Small intestine	1 (2.4)
Ovarian	1 (2.4)
Pulmonary carcinosarcoma	1 (2.4)
Carcinoma of the skin	1 (2.4)
Cholangiocarcinoma	1 (2.4)
Fusion partner	41 (100.0)
NCOA4	16 (39.0)
CCDC6	6 (14.6)
KIF5B	4 (9.8)
RET gene rearrangement[f]	2 (4.9)
Other[g]	13 (31.7)
Stage at entry	
Stage II	1 (2.4)
Stage III	3 (7.3)
Stage IV	34 (82.9)
Missing	3 (7.3)
Months since initial diagnosis	
Mean (SD)	20.6 (18.6)
Median	17.40
Min-max	1.7-74.2
History of metastatic disease	39 (95.1)
Measurable disease (by Investigator assessment)	37 (90.2)
Measurable disease (by IRC assessment)	36 (87.8)

Abbreviations: IRC = independent review committee; max = maximum; min = minimum; N = number of patients; n = number of patients in the specific category; *RET* = REarranged during Transfection; SD = standard deviation.

Diagnosis of primary tumor type:

[a] Salivary gland adenocarcinoma (1) and cancer of parotid gland (3).

[b] Unknown primary (2) and urothelial or renal source suspected (1).

[c] Disseminated cutaneous juvenile xanthogranulomatosis.

[d] Atypical carcinoid tumor.
[e] Small bowel adenocarcinoma.
[f] For 1 patient, the fusion partner was identified as KIAA1217 based on the submitted genomic report.
[g] Additional fusion partners: ETV6 (n=2), CGNL1 (n=1), ERC1 (n=1), GPHN (n=1), PRKAR1A (n=1), SPECC1L (n=1), TFG (n=1), GOLGA5 (n=1), RASAL2 (n=1), TAF3 (n=1), TRIM24 (n=1), and TRIM33 (n=1).

Data cutoff date: 24 September 2021.
Source: Module 2.7.3 SCE Table 2.7.3.4

Of the 41 patients in the Tissue-Agnostic Efficacy Population, 37 patients (90.2%) received prior systemic therapy, with a median of 2 prior lines of therapy (range: 0 to 9), including 68.3% of patients who received selpercatinib in the third or greater line setting:

9 (22.0%) received 1 prior line of therapy
15 (36.6%) received 2 prior lines of therapy, and
13 (31.7%) received 3 or more prior lines of therapy.

At the time of study enrollment, there were 4 patients who were treatment naive and were deemed by the Investigator to have no satisfactory standard-of-care therapeutic options:

2 patients with cancers of unknown primary origin, and
2 patients with xanthogranuloma.

The Applicant's Position:

Overall, the types of tumors and their frequencies in the **Tissue-Agnostic Efficacy Population** is reflective of the expected distribution in the broader US population. This **Tissue-Agnostic Efficacy Population** was heavily pretreated (the majority of patients received selpercatinib in the third or greater line setting).

The FDA's Assessment:

FDA agrees with the Applicant's description of other baseline characteristics of the patients enrolled in LIBRETTO-001. The small sample sizes of rare tumor types are similar to other tissue agnostic approvals.

Of the 41 patients in the Tissue-Agnostic Efficacy Population, 14 tumor types were represented (range 1 to 11 patients per tumor type), including: pancreatic, colorectal, salivary gland, unknown primary, breast, sarcoma, xanthogranuloma, carcinoid (bronchial), ovarian, small intestine, cholangiocarcinoma, pulmonary carcinosarcoma, rectal neuroendocrine and carcinoma of the skin.

There were five patients included in the Tissue-Agnostic Efficacy Population who did not have measurable disease per IRC. The tumor types for these 5 patients are as follows: two patients with xanthogranuloma, 1 patient with breast cancer, 1 patient with pulmonary carcinosarcoma, and 1 patient with salivary cancer.

Most patients were heavily pre-treated with a median of 2 prior therapies (range 0 to 9). Most patients (95%) had metastatic disease; one patient had Stage III colorectal cancer and one patient had xanthogranuloma of unknown stage. Per the protocol, patients were required to have progressed on or were intolerant to prior standard of care therapy(ies) or met one of the following criteria:

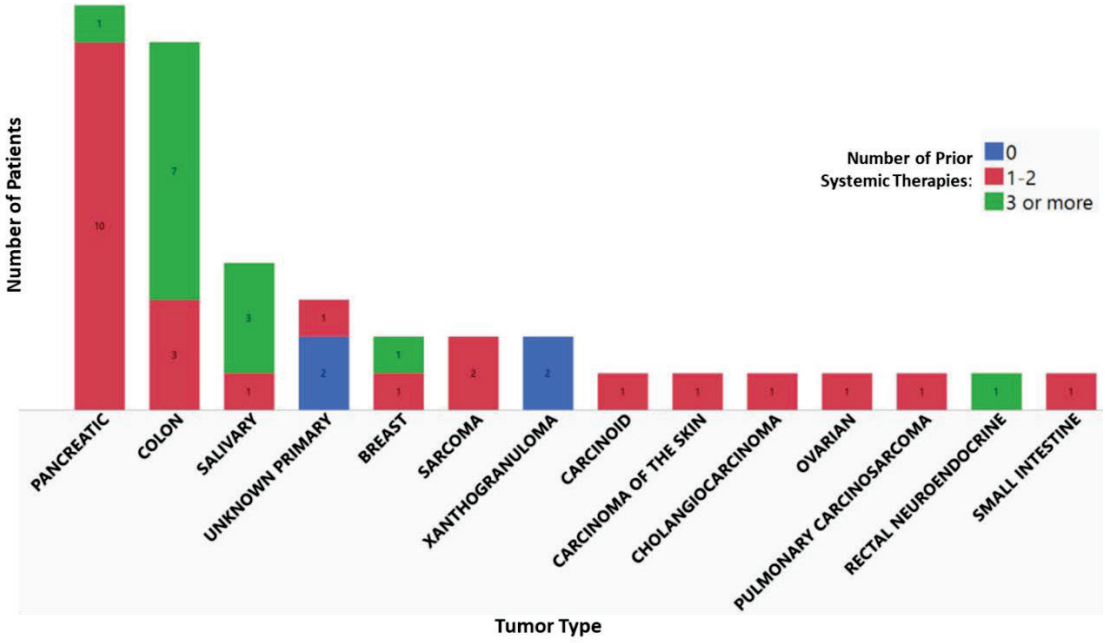
- No standard therapy existed, or
- In the opinion of the Investigator is not a candidate for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or
- The patient declined standard therapy

Inclusion also required specific prior systemic therapy regimens as follows:

- For colorectal cancer, fluoropyrimidine-based chemotherapy, with or without anti-VEGF-directed therapy or anti-EGFR-directed therapy as appropriate for the disease
- For pancreatic cancer, fluoropyrimidine-based, gemcitabine-based, or S-1 chemotherapy
- For breast cancer, anthracycline, taxane, HER2-directed therapy and/or hormonal therapy or other standard therapy appropriate for the disease
- For other tumor types, prior standard therapy for the disease

Figure 8-2 includes the 14 tumor types in decreasing incidence and number of prior therapies for each patient by tumor type.

Figure 8-2: **FDA Analysis of Tissue-Agnostic Efficacy Population by Tumor Type and Number of Prior Therapies**



Source: adsl.xpt

To further evaluate whether the *RET* fusion-positive patient population enrolled in LIBRETTO-001 reflects the broader population of patients with RET fusion-positive tumors, the Applicant provided a list of tumor types associated with RET fusions identified using the GENIE cBioPortal for Cancer Genomics (**Figure 8-3**). This database contains a biomarker screening sample size of 111,222 patients.

Figure 8-3: Frequency of Total RET Fusion Positive Patients in LIBRETTO-001 vs. GENIE cBioPortal for Cancer Genomics (Source: Applicant's Pre-sNDA Briefing Document submitted December 21, 2021, Table 6.8, page 43)

	Frequency of Total *RET* Fusion-Positive Patients (%)	
Tumor Type	**cBIO N=257**	**LIBRETTO-001 N=461**
NSCLC	54.5	78.1
Thyroid	27.6	12.1
Colorectal	3.9	2.2
Esophagogastric	2.7	-[a]
Unknown primary	2.3	0.7[b]
Breast	1.6	0.4
Hepatobiliary	1.2	0.4[c]
Glioma	1.2	-
Soft tissue sarcoma	0.8	0.7
Histiocytosis	0.8	0.4[d]
Miscellaneous brain tumor	0.4	-
Nerve sheath tumor	0.4	-
Small cell lung cancer	0.4	-
Salivary gland cancer	0.4	0.9[e]
Skin cancer	0.4	0.4
Bone cancer	0.4	-
Prostate cancer	0.4	-
Pancreatic cancer	0.4	2.6
Small intestine	-	0.2[f]
Rectal neuroendocrine	-	0.2
Ovarian	-	0.2
Pulmonary carcinosarcoma	-	0.2
Carcinoid	-	0.2[g]

Abbreviations: N = number of patients in the population; NSCLC = non-small cell lung cancer.

a 1 patient enrolled in LIBRETTO-001 with esophagogastric cancer died prior to receiving treatment with selpercatinib.

b Unknown primary and urothelial or renal source suspected.

c Cholangiocarcinoma.

d Xanthogranuloma - disseminated cutaneous juvenile xanthogranulomatosis.

e Salivary gland adenocarcinoma and cancer of parotid gland.

f Small bowel adenocarcinoma.

g Atypical carcinoid tumor.

Overall, the tissue-agnostic dataset in LIBRETTO-001 is reflective of the expected distribution and frequency of tumor types harboring RET fusions observed in the broader population. No patients with esophagogastric cancer or glioma were enrolled in this study, but 5 additional tumor types not included in the cBIO database were included as you can see at the bottom of the list. Due to the rarity of RET fusions, some population differences between datasets may be

expected.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance

At the time of data cutoff, 21 (46.7%) patients in the **Tissue-Agnostic Safety Population** were still on treatment. The median relative selpercatinib dose intensity in the **Tissue-Agnostic Safety Population** was high (97.8%) and consistent with the **Overall Safety Population** (94.5%). These data are provided in Table 2.7.4.2.

Concomitant Medications

The most frequently used therapeutic classes of concomitant medications in the *RET* fusion-positive Tissue-Agnostic Safety Analysis Set included natural opium alkalides (51.1%), serotonin (5HT3) antagonists (42.2%), anilides (40.0%), and glucocorticoids (40.0%). These data are provided in section 4.5 of the Tissue-Agnostic Interim CSR synopsis.

Rescue Medication Use

Not applicable

The Applicant's Position:

Treatment compliance in this study was high. The therapeutic classes of concomitant medication used were appropriate and were not considered to have impacted study results.

The FDA's Assessment:

FDA agrees with the Applicant's position. The median relative dose intensity (actual dose intensity [ADI]/planned dose intensity [PDI])×100) was 97.8%. All patients took concomitant medications, most commonly opioids, serotonin antagonists, paracetamol/acetaminophen, and steroids. These medications are unlikely to have impacted study results.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Summaries of the ORR, BOR, DOR, DCR, and CBR for the Tissue-Agnostic Efficacy Analysis Set are provided in Table 8.6.
In the **Tissue-Agnostic Efficacy Population** an ORR of 44% (n=18) was observed as determined by both IRC and investigator, including 2 patients who achieved CR.

**Table 8-6. Best Overall Response
Tissue-Agnostic Efficacy Analysis Set**

	RET Fusion-Positive Tissue-Agnostic Solid Tumors N=41	
	IRC Assessment	**Investigator Assessment**
Objective Response Rate[a,b]		
n (%)	18 (43.9)	18 (43.9)
95% CI	(28.5, 60.3)	(28.5, 60.3)
Best Overall Response, n (%)		
Complete response	2 (4.9)	2 (4.9)
Partial response	16 (39.0)	16 (39.0)
Stable disease	14 (34.1)	13 (31.7)
SD16+[c]	8 (19.5)	8 (19.5)
Progressive disease	3 (7.3)	7 (17.1)
Not evaluable	6 (14.6)	3 (7.3)
Clinical Benefit Rate (CR + PR + SD16+[c])[d]		
n (%)	26 (63.4)	26 (63.4)
95% CI[b]	(46.9, 77.9)	(46.9, 77.9)
Disease Control Rate (CR + PR + SD)		
n (%)	32 (78.0)	31 (75.6)
95% CI[b]	(62.4, 89.4)	(59.7, 87.6)
Duration of Response[e,f]		
Responders, n	18	18
Median in months (95% CI)	24.54 (9.2, NE)	18.43 (9.2, NE)
Range in months	2.3+, 38.3+	2.3+, 38.3+
Censored, n (%)[f]	11 (61.1)	9 (50.0)
Reason Censored		
Alive without documented disease progression	9 (50.0)	7 (38.9)
Subsequent anticancer therapy or cancer-related surgery without PD	1 (5.6)	1 (5.6)
Died or documented PD after missing 2 or more consecutive visits	1 (5.6)	1 (5.6)
Remaining in Response[e,g]		
At 6 months, % (95% CI)	81.1 (51.9, 93.5)	81.9 (53.8, 93.8)
At 12 months, % (95% CI)	73.7 (43.9, 89.3)	60.1 (31.3, 80.0)
Duration of Follow-Up (months)[e]		
Median	14.88	14.88

Abbreviations: + = censored observation; CI = confidence interval; CR = complete response; IRC = independent review committee; N = number of patients in the population; n = number of patients per category; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; RET = REarranged during Transfection; SD = stable disease; SD16 = stable disease lasting 16 or more weeks.

a ORR is defined as the proportion of patients with best overall response of a confirmed CR or PR. Response was confirmed by a repeat assessment after 28 or more days.

b 95% CI was calculated using the Clopper-Pearson method.

c SD16+ indicates SD lasting 16 or more weeks following initiation of selpercatinib until the criteria for disease progression was first met.
d Clinical benefit rate (%) is defined as the proportion of patients with best overall response of a confirmed CR, PR, or SD lasting 16 or more weeks (SD16+ weeks). SD was measured from the date of the first dose of selpercatinib until the criteria for disease progression or death was first met.
e Estimate based on the Kaplan-Meier method.
f 95% CI was calculated using the Brookmeyer and Crowley method.
g 95% CI was calculated using the Greenwood's formula.
Note: Censored patients are represented as a percentage of responders by IRC assessment (N=18) and Investigator assessment (N=18).
Data cutoff date: 24 September 2021.
Source: 2.7.3 SCE Table 2.7.3.5

The median DOR was

24.54 months (95% CI: 9.2, NE), with a median follow-up of 14.88 months by IRC
9 patients (50.0%) remained in response at the cutoff date, and
18.43 months (95% CI: 9.2, NE), with a median follow-up of 14.88 months by Investigator
7 patients (38.9%) remained in response at the cutoff date.

Subgroup Efficacy

Analyses by demographic characteristics due to the limited number of patients in each subgroup are not informative. A summary of responses by tumor type are provided in Table 8.7.

Table 8-7. Response by IRC by Tumor type

	N	% ORR (95% CI)	Median DOR in Months (Range)[a]	% CBR (95% CI)	% DCR (95% CI)
Tissue-agnostic Efficacy Population	41	43.9 (28.47, 60.25)	24.54 (2.30+, 38.34+)	63.4 (46.94, 77.88	78.0 (62.39, 89.44
Pancreatic	11	54.5 (23.38, 83.25)	NR (2.50, 38.34+)	63.6 (30.79, 89.07)	72.7 (39.03, 93.98)
Colorectal	10	20.0 (2.52, 55.61)	9.43 (5.55, 13.31)	70.0 (34.75, 93.33)	90.0 (55.50, 99.75)
Salivary	4	50.0 (6.76, 93.24)	NR (5.72, 28.78+)	75.0 (19.41, 99.37)	100.0 (39.76, 100.00)
Unknown primary	3	33.3 (0.84, 90.57)	9.23	66.7 (9.43, 99.16)	100.0 (29.24, 100.00)
Breast	2	PR, CR	17.28 (2.30+, 17.28)	100.0 (15.81, 100.00)	100.0 (15.81, 100.00)
Sarcoma	2	PR, SD	14.88+	50.0 (1.26, 98.74)	100.0 (15.81, 100.00)

Xanthogranuloma	2	NE. NE	NA	0.0 (0.00, 84.19)	0.0 (0.00, 84.19
Carcinoid	1	PR	24.11+	100.0 (2.50, 100.00)	100.0 (2.50, 100.00)
Ovarian	1	PR	14.52+	100.0 (2.50, 100.00)	100.0 (2.50, 100.00)
Small intestine	1	CR	24.54	100.0 (2.50, 100.00)	100.0 (2.50, 100.00)
Cholangiocarcinoma	1	PR	5.55+	100.0 (2.50, 100.00)	100.0 (2.50, 100.00)
Pulmonary carcinosarcoma	1	NE	NA	0.0 (0.00, 97.50)	0.0 (0.00, 97.50)
Rectal neuroendocrine	1	NE	NA	0.0 (0.00, 97.5)0	0.0 (0.00, 97.50)
Carcinoma of the skin	1	NE	NA	0.0 (0.00, 97.50)	0.0 (0.00, 97.50)

Abbreviations: + = censored observation; CBR = clinical benefit rate; CI = confidence interval; CR = complete response; DCR = disease control rate; DOR = duration of response; IRC = Independent Review Committee; N = number of participants per primary diagnosis; NA = not applicable; NE = not estimable; NR = not reached; ORR = objective response rate; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] Range is provided when more than 1 responder is present.

Efficacy-eligible patients are defined as the patients whose first dose date was on or before 24 March 2021.
Based on RECIST version 1.1.
Source: Module 2.5 CO Table 2.5.4.2

Overall, IRC assessment determined that

18 patients across 10 of the 14 tissue-agnostic tumor types demonstrated responses; these responses were observed for all tumor types, evaluable by imaging, with a sample size of 2 patients or more
2 patients had a CR (breast and small intestine), and
16 patients had a PR (breast, carcinoid, cholangiocarcinoma, colon, ovarian, pancreatic, salivary, sarcoma, and unknown primary).

Intrapatient Analysis

Responses to selpercatinib were seen in 17 of the 37 patients who received prior systemic therapy, leading to an ORR of 45.9% based on Investigator assessment. The ORR was 18.9% (7 of the 37 patients) for the last prior therapy. Responses with selpercatinib treatment were demonstrated regardless of whether responses to prior therapies were observed. Of the 17 responders to selpercatinib treatment, 15 did not respond to the last prior therapy, reflecting the potential for selpercatinib to benefit patients with refractory disease.
These data are provided in Module 2.7.3 Table 2.7.3.8 and Table 2.7.3.9.

Best change in tumor size

Thirty-five patients were eligible for change in tumor size analysis, of which 28 (80%) patients demonstrated a reduction in tumor size from baseline, as determined by IRC assessment. These data are provided in Module 2.7.3 Section 2.7.3.2.1.2.1.

The Applicant's Position:

Overall, the efficacy results demonstrate a strong response to selpercatinib treatment in a heavily pretreated patient population including many difficult to treat tumor types. A clinically meaningful response rate was observed for the overall **Tissue-Agnostic Efficacy Population**, with responses across 10 of the 14 tissue-agnostic tumor types and for all tumor types evaluable by imaging with a sample size of 2 patients or more.
In most cancer treatment settings, response rate declines with subsequent lines of treatment; however benefit to selpercatinib is observed regardless of whether a patient responded to their prior therapy or not. Patients in the LIBRETTO-001 **Tissue-Agnostic Efficacy Population** were heavily pretreated yet exhibited ORRs better than recommended second or greater therapy lines in almost all cases
Over 60% of **Tissue-Agnostic Efficacy Population** patients saw clinical benefit after administration of selpercatinib. Responses were durable with over 70% continuing to show response at 12 months with a long median follow-up time of almost 15 months.
The totality of data presented shows that selpercatinib, which targets the oncogenic driver in these tumors, provides durable response rates and high clinical benefit for patients with *RET* fusion-positive solid tumors after treatment with current standard-of-care agents that do not target RET.

The FDA's Assessment:
FDA generally agrees with the Applicant's summary of ORR and DOR by BIRC by tumor type. Patients with 10 of 14 tumor types with a variety of fusion partners had objective responses by BIRC, including patients with the following tumors: pancreatic, colorectal, salivary, unknown primary, breast, soft tissue sarcoma, bronchial carcinoid, ovarian, small intestine, and cholangiocarcinoma.

The confirmed ORR per RECIST 1.1 as determined by BIRC was 44% (95% CI 28, 60) with median DOR of 24.5 months (95% CI 9.2, NE). Two patients had complete responses, including one patient with breast cancer and one patient with small bowel adenocarcinoma. FDA notes that the sponsor's calculation for median follow-up for the duration of response uses the reverse Kaplan Meier method.

The observed proportion of patients remaining in response per BIRC at 6 months was 12/18

(67%, 95% CI: 41, 87). The observed proportion of patients remaining in response per BIRC at 12 months was 10/18 (56%, 95% CI: 31, 56). These differ from the sponsor's estimates presented in the preceding section which are based on the Kaplan Meier method.

Although the results show that treatment with selpercatinib results in durable overall responses in patients with a variety of tumor types, there is insufficient clinical experience to definitively conclude that the response rates observed are consistent across all *RET*-fusion positive cancers. Some of the tumors are only represented by 1 or 2 patients and for some tumor types the response was not evaluable; therefore, the results may not be representative of all patients with that particular tumor type.

Regarding the Applicant's intrapatient analysis of response to prior therapies, FDA's comments will focus on response per BIRC since that is the primary interpretation for the response data in this study. Of the 30 patients who did not respond to prior systematic therapy, 12 did not respond to selpercatinib per BIRC. Of the 18 patients who responded to selpercatinib, 3 had responded to prior therapy.

FDA does not consider stable disease in a single-arm trial to be a direct measure of treatment activity or efficacy, and the absence of a control arm makes analyses that include stable disease, such as clinical benefit rate, uninterpretable.

Five patients in the Tissue Agnostic Efficacy Analysis set (n=41) were **unevaluable per BIRC**, including two patients with xanthogranuloma (due to skin-only disease), one patient with pulmonary carcinosarcoma (no post-baseline imaging, discontinued due to AE), one patient with rectal neuroendocrine tumor (investigator determined progressive disease vs. BIRC determined stable disease, and there was no follow-up scan to confirm stable disease), and one patient with carcinoma of the skin (no post-baseline imaging, patient withdrew consent).

Four patients included in the Tissue Agnostic Safety Analysis set (n=45) were not included in the Tissue Agnostic Efficacy Analysis set (n=41) due to insufficient follow-up time. Three of the patients excluded from the efficacy analysis set had measurable disease per investigator. The best overall responses by investigator per RECIST 1.1 for the three patients excluded from the efficacy set with measurable disease were PR, SD, and NE at the time of the data cut-off. The patient without measurable disease also had a best overall response of NE.

Five patients in the Tissue Agnostic Efficacy Analysis set (n=41) had **non-measurable disease per BIRC**. These included 2 patients with xanthogranuloma (due to skin-only disease), one patient with pulmonary carcinosarcoma, one patient with breast cancer, and one patient with salivary gland cancer. According to RECIST 1.1, patients with nonmeasurable disease are evaluable for tumor response assessment, but in contrast to measurable disease, where a PR

can be achieved based on meeting a threshold for a change in tumor size, the assessment options for nonmeasurable disease are limited to CR, non-CR/non-PD, PD, and NE. The patient with breast cancer had a best overall response of CR per BIRC and the patient with salivary gland cancer had a best overall response of non-CR/non-PD per BIRC. A sensitivity analysis including only patients with measurable disease per BIRC (n=35) showed ORR 47% (95% CI 30, 65), which is similar to the overall ORR for the entire Tissue Agnostic Efficacy Analysis population.

Patients had a variety of ***RET* gene fusions partners** which varied across and within tumor types. Table 8.8 summarizes ORR by fusion partner.

Table 8-8: FDA Analysis of ORR by RET Gene Fusion Partner for the Tissue Agnostic Efficacy Analysis population (n=41)

RET fusion partner	N	Responders	ORR (95% CI)	Median DOR in months (Range)
NCOA4	16	5	31% (11, 59)	24.5 (5.5, 28.8+)
KIF5B	4	1	25% (0.6, 81)	9.2
CCDC6	6	4	67% (22, 96)	17.3 (2.3+, 24.1+)
Other	14	8	57% (29, 82)	NR (2.5, 38.3+)
Unknown	1	0	0	NA

Source: adpf.xpt, adrs.xpt, adtte.xpt

While the patients with NCOA4 and KIF5B fusion partners have lower numerical ORRs than patients with CCDC6 or other fusion partners, due to the small number of patients in each subgroup, no conclusions can be drawn regarding differences in efficacy by fusion partner for the tissue agnostic population.

For reference, in sNDA 213246 supplement 7 (the application intended to support regular approval of selpercatinib in patients with *RET* fusion-positive NSCLC), an analysis of ORR by fusion partner was performed for patients with *RET* fusion-positive NSCLC enrolled in LIBRETTO-001. In this population, the NCOA4 fusion was rare (6 of 316 efficacy-evaluable patients), and was grouped with other non-KIF5B/non-CCDC6 fusion partners. The ORR for the group of patients with non-KIF5B/non-CCDC6 fusion partners was 48% (95% CI: 26, 70) among previously-treated patients (n = 21) and 67% (95% CI: 9, 99) among treatment-naïve patients (n

= 3). The ORR for patients with KIF5B fusion partners was 56% (95% CI: 47, 64) among previously-treated patients (n = 153) and 79% (95% CI: 65, 90) among treatment-naïve patients (n = 48).

In the tissue agnostic efficacy population, The NCOA4 fusion type was most commonly seen in patients with colon cancer; refer to the discussion below ("FDA Analysis of Response by Tumor Type) and to Section 6.3.2.1 for additional information.

There is some discrepancy in the estimates for median duration of response as assessed by BIRC and investigator per RECIST 1.1, with BIRC reporting a longer median duration of response. There are two major factors that contribute to this difference:

1) Responses per BIRC and investigator had a concordance of 90%; that is, there are discrepancies in the best overall response per BIRC and investigator for 4 patients. One of the patients identified as a responder per investigator but not by BIRC had xanthogranuloma; this patient had a best overall response of CR per investigator and NE per BIRC.
2) There were 5 patients who had longer event times per BIRC than by investigator, which is suggestive of informative censoring, and 1 patient with a longer event time per investigator than by BIRC (Table 8.9). Of note, the patient with small intestine cancer had a longer event time per BIRC than by investigator due to discrepancy in the start of response, as the investigator noted an initial response at a later time point than the BIRC.

Table 8-9: **FDA Analysis of Event Type and Time for Patients with Discrepancy in Event Time per BIRC vs. Investigator**

Tumor Type	Event Type	Event time per BIRC in months	Event time per investigator in months
Small Intestine	Death	24.54	22.57
Carcinoid	Censored, alive without documented disease progression	24.11	18.60
Colon	Progressive Disease	13.31	9.79
Colon	Progressive Disease	5.55	3.71
Pancreatic	Censored, alive	14.75	11.99

	without documented disease progression		
Breast	Progressive disease	17.28	18.43

Source: adtte.xpt

FDA Analysis of Responses by Tumor Type

Pancreatic Adenocarcinoma

The most common tumor type in the Tissue Agnostic Efficacy Analysis population was pancreatic adenocarcinoma. Of the 11 patients with pancreatic cancer, 6 had partial responses (ORR 55% [95% CI 23, 83]) with durations of response ranging from 2 to 38 months. All patients had Stage IV disease and had received 1-4 prior lines of therapy, including standard first line therapy (Table 8.10). The lower bound of the 95% CI of ORR in this patient population is greater than the reported response rates to available second line therapies (ORR 13-16%), with responses ongoing in all but one patient. Three responders had durations of response of >1 year, which is greater than the reported median overall survival for patients with recurrent advanced pancreatic cancer (4 to 12 months; Chiorean et al, 2016, Citterio et al, 2018).

Table 8-10: FDA Summary of Patients with Pancreatic Cancer by Responders vs. Non-responders

Age (years) / Sex / Race	*RET* fusion partner	Best Overall Response by BIRC	Prior therapies (1L / 2L / 3L / 4L)
Responders			
(b) (6)	PRKAR1A	PR	FOLFIRINOX / FOLFIRI
	SPECC1L	PR	FOLFIRINOX / nab-paclitaxel + gemcitabine
	CGNL1	PR	FOLFIRINOX

(b) (6)	TRIM24	PR	S1 chemotherapy / FOLFIRINOX
	GPHN	PR	FOLFIRINOX / FOLFIRI
	CCDC6	PR	FOLFIRINOX / cisplatin + doxorubicin / gemcitabine + nab-paclitaxel / nivolumab + ipilimumab
Non-Responders			
(b) (6)	NCOA4	SD	FOLFIRINOX / FOLFIRI
	TFG	SD	FOLFIRINOX / cabozantinib
	ERC1	PD	Cisplatin + etoposide / carboplatin + etoposide
	NCOA4	NE	FOLFOX + bevacizumab / cisplatin + IRI
	CCDC6	PD	Cisplatin + gemcitabine

FOLFOX = 5-FU + oxaliplatin; FOLFIRI = 5-FU + irinotecan; FOLFIRINOX = 5-FU + oxaliplatin + irinotecan; CAPOX = capecitabine + oxaliplatin; CAPE = capecitabine; IRI = irinotecan; BEV = bevacizumab; S1 chemotherapy = tegafur/gimeracil/oteracil; Lonsurf = trifluridine + tipiracil

Source: adsl.xpt, Clinical Study Report

Colorectal Cancer

The second most common tumor type in the Tissue Agnostic Efficacy Analysis population was colorectal cancer. Of the 10 patients with colorectal cancer, 2 had partial responses (ORR 20% [95% CI 3, 56]) with durations of response ranging from 5.6 to 13.3 months. All patients had

Stage IV disease, except one patient with Stage III disease. These patients were heavily pre-treated, with a median of 3.5 prior lines of therapy (range 2 to 9). All patients received FOLFOX, FOLFIRI, or CAPEOX, with or without bevacizumab, as recommended by NCCN as first or second therapy (Table 8.11).

The observed response rate in this patient population is lower than that observed with the other more common tumor types with *RET* fusions (i.e., NSCLC, thyroid cancer, and pancreatic cancer). This finding is likely multifactorial, including the relatively small number of patients with this tumor type enrolled in LIBRETTO-001, the high number of prior therapies in this population (median 3.5, compared to median 2 in overall tissue agnostic population), and the aggressive nature of recurrent colorectal cancer. In the second or greater line of therapy for patients with advanced colorectal cancer, reported ORRs range from 1% to 22% (Refer to Table 2.2).

While most patients (9/10) with colorectal cancer harbored a *RET* fusion with the NCOA4 fusion partner, it is not clear that this fusion partner is necessarily associated with non-responsiveness. Other patients with different tumor types who harbored a RET-NCOA4 fusion did have responses (CR in patient with small bowel adenocarcinoma; PR in patient with salivary gland cancer). Published literature suggests the specific fusion partner upstream of RET may regulate the degree of RET transcription, which may modulate the amount of RET oncoprotein that needs to be overcome by tyrosine-kinase inhibition (Richardson et al, 2009; Kohno et al, 2012).

Regarding potentially significant genetic co-alterations, one patient with CRC also harbored a potential *KRAS* driver alteration and one patient had microsatellite instability (MSI)-high status. While there are acquired resistance mutations reported with selpercatinib, there do not appear to be any clear intrinsic resistance mutations currently known. See Section 6.3.2.1 regarding additional information on genomic profiling data.

In summary, while the observed response rate in this patient population is lower than some other tumor types included in LIBRETTO-001, there were patients with CRC who responded to selpercatinib, with response durations ranging from 5 to 13 months, suggesting that selpercatinib may provide an additional option for these patients with poor prognosis and unmet clinical need.

Table 8-11: FDA Summary of Patients with Colorectal Cancer by Responders vs. Non-responders

Age (years) / Sex / Race	*RET* fusion partner	Best Overall Response by	Prior therapies

		BIRC	(1L / 2L / 3L / … / 9L)
Responders			
(b) (6)	NCOA4	PR	FOLFOX / FOLFIRI + BEV / CAPE
	NCOA4	PR	CAPOX / FOLFIRI + panitumumab / FOLFIRINOX + BEV / FOLFOX + BEV / BEV
Non-Responders			
(b) (6)	NCOA4	PD	FOLFOX / FOLFOX + panitumumab / 5-FU + panitumumab
	NCOA4	SD	CAPOX + BEV / CAPE + BEV / IRI / panitumumab / 5-FU / panitumumab / CAPOX + BEV / Lonsurf / CAPOX + BEV
	NCOA4	SD	FOLFIRI + cetuximab / IRI + cetuximab / Lonsurf / atezolizumab
	CCDC6	SD	CAPOX / ipilimumab + nivolumab
	NCOA4	SD	FOLFOX / CAPE
	NCOA4	SD	FOLFOX + BEV / CAPE + BEV / 5-FU + BEV / FOLFIRI + panitumumab / BEV
	NCOA4	SD	5-FU / FOLFIRI

(b) (6)	NCOA4	SD	CAPOX / S1 + IRI + panitumumab / regorafenib / Lonsurf + BEV

FOLFOX = 5-FU + oxaliplatin; FOLFIRI = 5-FU + irinotecan; FOLFIRINOX = 5-FU + oxaliplatin + irinotecan; CAPOX = capecitabine + oxaliplatin; CAPE = capecitabine; IRI = irinotecan; BEV = bevacizumab; S1 chemotherapy = tegafur/gimeracil/oteracil; Lonsurf = trifluridine + tipiracil

Source: adsl.xpt, Clinical Study Report

Salivary Gland Cancer

The third most common tumor type in the Tissue Agnostic Efficacy Analysis population was salivary gland cancer. Of the 4 patients with salivary gland cancer, 2 had partial responses (ORR 50% [95% CI 7, 93]) with durations of response ranging from 5.7 to 28.8 months (Table 8.12).

NCCN states that the choice of systemic therapy for salivary gland cancer should be individualized based on individual patient characteristics and there are no preferred first line regimens. Chemotherapy regimens may include cisplatin or carboplatin, paclitaxel, vinorelbine, doxorubicin, cyclophosphamide, gemcitabine.

The 5-year survival rate for patients with metastatic salivary gland cancer is 44% (American Cancer Society, 2022). In the recurrent setting, reported response rates to a variety of investigational agents range from 0% to 24% (Chintakuntlawar et al, 2016). While only four patients with salivary gland cancer were enrolled in LIBRETTO-001, it does appear that these patients may have durable responses to selpercatinib.

Table 8-12: FDA Summary of Patients with Salivary Gland Cancer by Responders vs. Non-responders

Age (years) / Sex / Race	*RET* fusion partner	Best Overall Response by BIRC	Prior therapies (1L / 2L / 3L)
Responders			

(b) (6)	ETV6	PR	Cisplatin / carboplatin + pemetrexed + pembrolizumab / pembrolizumab
	NCOA4	PR	Cisplatin
Non-Responders			
(b) (6)	NCOA4	Non-CR/Non-PD	Bicalutamide / leuproelin / enzalutamide
	KIAA1217	SD	Cisplatin + cetuximab + 5-FU / nivolumab / paclitaxel + cetuximab

Source: adsl.xpt, Clinical Study Report

Other Solid Tumors in Efficacy Population

Sixteen patients with other tumor types comprised the remainder of the Tissue Agnostic Efficacy Analysis population, with 1 to 3 patients per tumor type. Eight of those patients had objective responses (Table 8.13). The small number of patients per tumor type limit the ability to draw conclusions regarding the representativeness to all patients with that particular tumor type.

Table 8-13: FDA Summary of Patients with Solid Tumors Other than Pancreatic, Colorectal and Salivary Gland Cancer (Responders, Non-Responders, Unevaluable Patients)

Tumor Type	Age (years) / Sex / Race	*RET* fusion partner	Best Overall Response by BIRC	Prior therapies (1L / 2L / 3L)
Responders				
Unknown Primary	(b) (6)	KIF5B	PR	Carboplatin + paclitaxel /

				cisplatin + gemcitabine
Breast (HER2 negative, BRCA1/2 negative)	(b) (6)	CCDC6	PR	Cyclophosphamide + docetaxel / cyclophosphamide + doxorubicin + paclitaxel / paclitaxel / letrozole / fulvestrant + palbociclib
Breast (HER2 negative, BRCA1/2 negative)		CCDC6	CR	Goserelin acetate + tamoxifen citrate
Soft tissue sarcoma (head/neck)		GOLGA5	PR	Doxorubicin
Carcinoid (atypical carcinoid of lung)		CCDC6	PR	Temozolomide + capecitabine
Ovarian (low grade serous carcinoma)		TRIM33	PR	Carboplatin + paclitaxel / letrozole
Small intestine (small bowel adenocarcinoma)		NCOA4	CR	FOLFOX / FOLFIRI + panitumumab
Cholangiocarcinoma		NCOA4	PR	Gemcitabine + S1 chemotherapy / cisplatin + gemcitabine
Non-Responders				
Unknown Primary (urothelial or renal	(b) (6)	KIF5B	SD	No prior therapy

source suspected)				
Unknown Primary	(b) (6)	KIF5B	SD	No prior therapy
Soft tissue sarcoma (thoracic)		RASAL2	SD	Anlotinib
Unevaluable by BIRC				
Xanthogranuloma (disseminated cutaneous juvenile xanthogranulomatosis)	(b) (6)	NCOA4	NE	No prior therapy
Xanthogranuloma (cutaneous juvenile xanthogranuloma)		ETV6	NE	No prior therapy
Pulmonary Carcinosarcoma		KIF5B	NE	Pembrolizumab / pemetrexed + carboplatin + pembrolizumab
Rectal Neuroendocrine		TAF3	NE	Everolimus / capecitabine + temozolomide / cisplatin + etoposide / regorafenib
Carcinoma of skin (adenosquamous carcinoma of left back)		RET gene rearrangement by FISH (no partner identified)	NE	Cemiplimab

FOLFOX = 5-FU + oxaliplatin; FOLFIRI = 5-FU + irinotecan; S1 chemotherapy = tegafur/gimeracil/oteracil

Source: adsl.xpt, Clinical Study Report

Data Quality and Integrity The Applicant's Position:

No issues relating to data integrity or quality were identified that would affect the efficacy results.

The FDA's Assessment:

FDA agrees with the Applicant's position. The data submitted were organized and adequate to perform a complete review of the efficacy of selpercatinib in patients with RET fusion-positive solid tumors. FDA issued information requests during the review cycle to obtain clarification and additional information regarding data included in the sNDA and all requests were addressed appropriately.

Efficacy Results – Secondary and other relevant endpoints

Data:

The Key secondary endpoints of DOR, CBR and DCR are presented above in table Table 8.6**.** PFS and OS are shown here.

Progression free survival

Median PFS by IRC assessment was 13.24 months (95% CI: 7.4, 26.2), with a median follow-up of 16.43 months. At the time of data cutoff, 34.1% of patients by IRC assessment were still on treatment, with no documented disease progression. These data are provided in Module 2.7.3 Section 2.7.3.2.1.2.3.

Overall survival

Median OS was 18.04 months (95% CI: 10.7, NE), with a median follow-up time of 18.76 months. The OS data are not yet mature, with a censoring rate of 56.1%. Approximately, half of the patients (47.4%) were alive at the 2-year landmark. These data are provided in Module 2.7.3 Section 2.7.3.2.1.2.4.

The Applicant's Position:

Results for the secondary endpoints are supportive of the results of the primary study endpoint.

The FDA's Assessment:
While FDA agrees with the reported median PFS and OS, the treatment effect on such time-to-event endpoints is uninterpretable in the context of a non-randomized trial due to a lack of appropriate comparator group.

Dose/Dose Response

Data:

Refer to section 6.2.2.1 above.

The Applicant's Position:

For the tissue-agnostic indication, the Sponsor recommends using the same weight-based dose regimen as NSCLC and TC, i.e. 120 mg BID (in patients <50 kg) and 160 mg BID (in patients ≥50 kg).

The FDA's Assessment:
FDA agrees with the Applicant's position. Refer to Section 6 for additional details.

One patient in the efficacy population did not receive at least one dose of selpercatinib 160mg BID (patient received 120 mg BID and never escalated to 160 mg BID). A sensitivity analysis excluding this patient showed a similar ORR of 45% (95% CI 29, 62) with the same median DOR (24.5 months) as the Tissue Agnostic Efficacy Population.

Durability of Response

Data:

Refer to data in Table 8.6.

The Applicant's Position:

Refer to efficacy results in Section 8.1.2

The FDA's Assessment:
Refer to FDA's Assessment of the Primary Efficacy results above.

Persistence of Effect

Data:

Not provided in this submission

The FDA's Assessment:
Not applicable

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

Not provided in this submission

The FDA's Assessment:
Not applicable

Additional Analyses Conducted on the Individual Trial

Data:

Not provided in this submission

The Applicant's Position:

The FDA's Assessment:
Not applicable

Integrated Review of Effectiveness

The FDA's Assessment:
The efficacy evaluation for this sNDA is based primarily on the analysis of 41 patients with *RET* fusion-positive solid tumors other than NSCLC and thyroid cancer enrolled in Study LIBRETTO-001 who received selpercatinib after having progressed on or following prior systemic treatment or who had no satisfactory alternative treatment options.

The primary evidence of effectiveness of selpercatinib was established by the demonstration of a clinically meaningful durable ORR in the primary analysis population. The confirmed ORR per RECIST 1.1 as determined by BIRC was 44% (95% CI 28, 60). As of the data cut-off date of September 24, 2021, the median DOR was 24.5 months (95% CI 9.2, NE). Additionally, 67% (95% CI 41, 87) and 56% (95% 31, 56) of patients remained in response at 6 and 12 months, respectively.

Patients with 10 of 14 tumor types with a variety of fusion partners had objective responses by BIRC, including patients with the following tumors: pancreatic, colorectal,

salivary, unknown primary, breast, soft tissue sarcoma, bronchial carcinoid, ovarian, small intestine, and cholangiocarcinoma. Patients were enrolled at sites distributed across multiple geographic regions (North America, Asia Pacific, Europe, and Middle East), including 63% of patients enrolled in the United States, ensuring that the results are largely applicable to the intended U.S. population.

Although the response rates for each tumor type were variable in the setting of small patient populations (range 1 to 11 patients per tumor type), FDA considered these data in the context of the existing approvals for RET fusion-positive NSCLC and thyroid cancer (Table 8.14). Overall response rates ranged from 61% to 100% in patients with RET fusion-positive NSCLC and thyroid cancer, tumor types more commonly characterized by this genetic alteration. Based on the totality of the data suggesting clinically meaningful response rates across tumor types, a tissue agnostic indication is appropriate.

Table 8-14: FDA Analysis of Overall Response Rate and Duration of Response by Indication for Selpercatinib

Selpercatinib Indication	N	ORR by BIRC (95% CI)	Median DOR, months (95% CI)	% w/ DOR ≥6 mos.
RET Fusion-Positive **Solid Tumors,** Previously treated or no satisfactory alternative treatment options	41	**44%** (28, 60)	25.4 (2.3, 38.3)	67%
RET Fusion-Positive **NSCLC**, Previously Treated with Platinum Chemotherapy	247	**61%** (55, 67)	28.6 (20, NE)	87%
RET Fusion-Positive **NSCLC**, Treatment-Naïve	69	**84%** (73, 92)	20.2 (13, NE)	88%
RET Fusion-Positive **Thyroid Cancer**, Previously Treated	19	**79%** (54, 94)	18.4 (7.6, NE)	87%
RET Fusion-Positive **Thyroid Cancer**, Systemic Therapy Naïve	8	**100%** (63, 100)	NE (NE, NE)	75%

Source: adrs.xpt, adtte.xpt RETEVMO Multidisciplinary Review (5/8/2020), sNDA 213246 Supplement 7 Review (9/21/2022)

The submitted evidence meets the statutory evidentiary standard for accelerated approval. An ORR of sufficient magnitude and duration is an endpoint reasonably likely to predict clinical benefit in patients with solid tumors, and this endpoint has supported the accelerated approvals of multiple other targeted therapies for patients with solid tumors harboring oncogenic driver mutations. The review team considers that the durable responses observed across multiple tumor types in Study LIBRETTO-001, in the setting of a genetically-based biologic rationale and the existing approvals in advanced *RET* fusion-positive NSCLC and thyroid cancer, provide evidence of a clinically meaningful benefit of selpercatinib in the rare, genetically defined subgroup of patients with locally advanced or metastatic *RET* fusion-positive solid tumors.

Assessment of Efficacy Across Trials

Efficacy data are provided from a single study.

Primary Endpoints

Not provided in this submission

The FDA's Assessment:
Not applicable

Secondary and Other Endpoints

Not provided in this submission

The FDA's Assessment:
Not applicable

Subpopulations

Not provided in this submission

The FDA's Assessment:
Not applicable

Additional Efficacy Considerations

The FDA's Assessment:
Not applicable

Integrated Assessment of Effectiveness

Not provided in this submission

The FDA's Assessment:
Not applicable as there is one clinical study assessing efficacy. Refer to the Integrated Review of Effectiveness.

Review of Safety

The Applicant's Position:

The safety of selpercatinib in patients with *RET* fusion-positive tissue-agnostic solid tumors (**Tissue-Agnostic Safety Population**) was evaluated in context with all patients who were administered at least one dose of selpercatinib regardless of RET alteration of tumor type (**Overall Safety Population**).
The latest data cutoff date for the **Overall Safety Population** is 15 June 2021 and is the same safety data that is presented in the recent NSCLC sNDA (seq 0586). The **Tissue-Agnostic Safety Population** data is presented from the 24 September 2021 data cutoff date. Between the two data cutoff dates only 2 additional patients with *RET* fusion-positive tissue-agnostic solid tumors enrolled in LIBRETTO-001 and therefore most patients in the **Tissue-Agnostic Safety Population** (N=45) are represented in the **Overall Safety Population** (n=43 of N=796) previously presented in the NSCLC sNDA.

The FDA's Assessment:
FDA agrees with the primary safety population as described by the Applicant. The **Overall Safety Population** comprises 796 patients with *RET*-altered advanced solid tumors who received selpercatinib in Study LIBRETTO-001. The **Tissue-Agnostic Safety Population** comprises 45 patients with *RET* fusion-positive advanced solid tumors other than NSCLC and thyroid cancer who received selpercatinib in Study LIBRETTO-001.

Safety Review Approach

The Applicant's Position:

The **Tissue-Agnostic Safety Population** and **Overall Safety Population** safety profiles were determined to be not notably different. While some differences were observed and discussed

in this clinical overview these differences were not unexpected considering the aggressive tumor types such as colorectal cancer and pancreatic cancer in the **Tissue-Agnostic Safety Population**. Selpercatinib is well tolerated across indications, even in heavily pretreated individuals, and has low rates of discontinuations due to selpercatinib-related AEs.

The FDA's Assessment:

FDA agrees that the safety profile of selpercatinib observed in the Tissue-Agnostic Safety Population (n=45) is reflective of the known safety profile of selpercatinib in other approved indications. No new safety signals for selpercatinib were identified during the course of this review.

The safety population used to inform the Warnings and Precautions section (Section 5) and Adverse Reactions section (Section 6) of the product labeling comprises 796 patients with advanced solid tumors harboring *RET* alterations who received at least one dose of selpercatinib in Study LOXO-RET-17001 (LIBRETTO-001), including 43 patients in the Tissue-Agnostic Safety Population enrolled prior to the data cut-off date of June 15, 2021.

The Tissue-Agnostic Safety Population (n=45) includes two additional patients who were enrolled between June 15, 2021 and the tissue agnostic efficacy data cut-off of September 24, 2021.

The safety results are viewed in the setting of the existing clinical experience with the product and its post-marketing safety database. As such, the review was carried out predominantly based on the review of the clinical study report and summary data provided by the sponsor.

Refer to the Clinical and Statistical Review of selpercatinib sNDA 213246 Supplement 7 for a full review of the Overall Safety Population (n=796).

Review of the Safety Database

Overall Exposure

Data:

Table 8-15 summarizes drug exposure and dose intensity for selpercatinib in the analyses with the data cutoff of 24 September 2021 for the **Tissue-Agnostic Safety Population** and 15 June 2021 for the **Overall Safety Population**.

Table 8-15. Selpercatinib Dose Intensity

	Tissue-Agnostic Safety Population N = 45	Overall Safety Population N = 796
Time on treatment (months)[a]		
Median	6.6	21.3
Min	0.6	0.1
Max	44.0	49.0
Relative dose intensity[b] (%)		
Mean (SD)	90.1 (13.8)	84.8 (19.1)
Median	97.8	94.5
Range	49.9-100.0	17.3-100.1
Relative dose intensity category, n (%)		
≥90%	32 (71.1)	468 (58.8)
75-<90%	5 (11.1)	121 (15.2)
50-<75%	7 (15.6)	145 (18.2)
<50%	1 (2.2)	62 (7.8)

Abbreviations: Max = maximum; Min = minimum; N = number of patients in the safety population; n = number of patients in the specific category; SD = standard deviation.

[a] Time on Treatment (TOT) (months) = (last dose date - first dose date + 1)/30.4375 for patients who discontinued selpercatinib as of the data cutoff date; TOT (months) = (data cutoff date - first dose date + 1)/30.4375 for subjects continuing to receive selpercatinib as of the data cutoff date.

[b] Relative dose intensity (%) = (actual dose intensity/planned dose intensity) × 100.

Percentage is calculated based on the number of patients in the column heading as the denominator.
Data cutoff dates: 24 Sep 2021 (**Tissue-Agnostic Safety Population**); 15 Jun 2021 (**Overall Safety Population**)
Source: Mod 2.7.4 SCS Table 2.7.4.2

The Applicant's Position:

Median dose intensity was high and similar across the two populations which provides evidence of selpercatinib's favourable tolerability.

The FDA's Assessment:

FDA agrees with the Applicant's position that the median relative dose intensity was high in both the Overall Safety Population (n=796) and the Tissue-Agnostic Safety Population (n=45). The median time on treatment was lower in the Tissue-Agnostic Safety Population (6.6 months) compared to the Overall Safety Population (21.3 months), which aligns with the timing of enrollment of patients with RET fusion positive solid tumors other than NSCLC and thyroid cancer.

Relevant characteristics of the safety population:

Data:

The median age of the **Tissue-Agnostic Safety Population** (53 years) was slightly younger than the **Overall Safety Population** (59 years). In particular, the pancreatic subpopulation had a median age of 45 years and represents approximately 25% of the **Tissue-Agnostic Safety Population**.
In total 14 unique tumor types are represented in the **Tissue-Agnostic Safety Population**. The majority of these tumors were Stage IV at study entry (84.4%) and almost all of the patients had a history of metastatic disease (95.6%).
The **Tissue-Agnostic Safety Population** was heavily pretreated and 91.1% of patients had received systemic treatment prior to LIBRETTO-001 enrolment compared to 74.5% in the **Overall Safety Population**. In the **Tissue-Agnostic Safety Population** 68.9% of patients were receiving selpercatinib as their 3rd or higher line of therapy compared to 45.6% in the **Overall Safety Population**.

The Applicant's Position
Selpercatinib is well tolerated across indications, even in heavily pretreated individuals.

The FDA's Assessment:
FDA agrees with the Applicant's position that the demographic characteristics are generally similar in the Overall Safety Population (n=796) and the Tissue-Agnostic Safety Population (n=45).

In the Overall Safety Population, the median age was 59 years (range: 15 to 92 years); 0.3% were pediatric patients 12 to 16 years of age; 66% were younger than 65 years of age and 34% were 65 years or older. Fifty-one percent were male; 68% were White, 23% were Asian, 3% were Black, and 5% were Hispanic/Latino ethnicity. In addition, 0.3% were American Indian or Alaska Native, 0.3% were Native Hawaiian or Other Pacific Islander, and 4% were identified as Other. Regarding region, 59% were from the US. Baseline ECOG performance status was 0 (37%), 1 (58%) or 2 (5%); 64% were never smokers, 32% former smokers, 3% current smokers. The most common tumors were NSCLC (45%), MTC (41%), and non-medullary thyroid carcinoma (7%); 98% had a history of metastatic disease. Prior therapies in the Overall Safety Population included systemic therapy (75%), surgery (65%) and radiation (46%). The median number of prior systemic regimens was 1 (range 0 to 15).

Adequacy of the safety database:

Data:
A total of 45 patients with *RET* fusion-positive solid tumors other than NSCLC and TC were available for safety analysis (**Tissue-Agnostic Safety Population**). This safety population is a

diverse population with data across 14 unique tumor types. Safety data of the **Tissue-Agnostic Safety Population** was reviewed in the context of the larger **Overall Safety Population** of 796 patients.

The Applicant's Position
The overall safety database for selpercatinib (which included 43 patients from the **Tissue-Agnostic Safety Population**) is sufficient to adequately characterize the safety profile.

The FDA's Assessment:
FDA agrees with the Applicant's position that the safety population studied in LIBRETTO-001 adequately represents the target population, including demographics, disease, and other baseline characteristics. The safety narratives were also adequate to allow further assessment of relevant safety signals.

Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:
Not applicable

The Applicant's Position:
There were no data issues identified. This sNDA submission contains all the required components of the electronic Common Technical Document (eCTD). Analysis-ready, efficacy and safety datasets, which support the efficacy and safety of selpercatinib for LOXO-RET-17001, are provided.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Categorization of Adverse Event

Data:

Evaluation of AEs
All patients who received at least 1 dose of study drug were evaluated for safety and toxicity.
Mapping of AE terms
Each NCI-CTCAE version 4.03 term reported by the investigator was mapped to the MedDRA version 21.0 preferred term (PT) and system organ class (SOC) of the corresponding MedDRA Lower Level Term (LLT), unless the reported CTCAE term was 'Other specify.' If the reported

CTCAE term was 'Other - specify,' the MedDRA LLT, PT, and SOC mapped from the verbatim AE term were used. All listings and summaries used the PT resulting from this process.

Composite terms

The PTs identified by medical evaluation as clinically identical or synonymous were grouped together under a single composite term. Composite terms are clinically synonymous PTs consolidated under a corresponding term to minimize the excess granularity of MedDRA PTs and to allow meaningful interpretation of data. Composite terms are *italicized.*

Evaluation of AESI

The safety evaluation plan also included analysis of AESI. Based upon considerations of preclinical toxicology and safety trends observed during the conduct of the ongoing LIBRETTO-001 study, the following event categories were deemed AESI:

liver injury

hypertension

drug hypersensitivity, and

QT prolongation.

The Applicant's Position:

All data were collected and assessed appropriately

The FDA's Assessment:

FDA agrees with the Applicant's position.

Routine Clinical Tests

Data:

Routine hematology, chemistry laboratory, and vital signs assessments were performed.

The Applicant's Position:

Assessment performed were appropriate

The FDA's Assessment:

FDA agrees with the Applicant's position.

Safety Results

Deaths

Data:

There were 7 (15.6%) deaths in the **Tissue-Agnostic Safety Population** within 28 days of last dose of selpercatinib (Table 8-16). Three (6.7%) of these were due to disease progression and 3 (6.7%) were due to a TEAE which were determined to be unrelated to selpercatinib treatment by the investigator (Table 8-16).
Eleven (24.4%) out of the 12 deaths which occurred 28 days or more after last dose of selpercatinib were related to disease progression. One death was due to an unknown cause and the site request for the death record was denied (Table 8-16). This patient stayed on treatment for 1.8 months and the death occurred 220 days after the last dose of selpercatinib.

Table 8-16. Summary of Deaths

	Tissue-Agnostic Safety Population N=45	Overall Safety Population N=796
Within 28 days of last dose, n (%)	7 (15.6)	56 (7.0)
Disease progression	3 (6.7)	19 (2.4)
Adverse event	3 (6.7)	34 (4.3)
Other	1 (2.2)[a]	3 (0.4)
More than 28 days after last dose, n (%)	12 (26.7)	137 (17.2)
Disease progression	11 (24.4)	109 (13.7)
Adverse event	0	10 (1.3)
Other	1 (2.2)	18 (2.3)

Abbreviations: N = number of patients in the safety population; n = number of patients in the specific category.
[a] Other included: Death due to disease progression and blockage of portal vein.
Note: Percentage is calculated based on the number of patients in the column heading as the denominator.
Data cutoff dates: 24 Sep 2021 (**Tissue-Agnostic Safety Population**); 15 Jun 2021 (**Overall Safety Population**)
SOURCE: Mod 2.7.4 SCS Table 2.7.4.10

The Applicant's Position:

Deaths in this study are as expected in oncology studies, with most deaths being due to disease progression. The frequency of deaths due to TEAEs was similar in the **Tissue-Agnostic Safety Population** and the **Overall Safety Population**

The FDA's Assessment:
FDA agrees with the Applicant's summary of deaths in the Overall Safety Population (n=796) and the Tissue-Agnostic Safety Population (n=45).

Regarding total deaths, 24% of patients in the Overall Safety Population and 42% of patients in the Tissue-Agnostic Safety Population died as of the data cut-off. The higher percentage of deaths in the Tissue-Agnostic Safety Population is likely due to the shorter expected overall survival of patients with those tumor types (primarily pancreatic and colorectal cancer) as compared to NSCLC and thyroid cancer.

Grade 5 TEAEs occurred in 3 patients (7%) in the Tissue-Agnostic Safety Population as of the data cut-off of September 24, 2021. FDA reviewed the narratives for each of these fatal TEAEs and Table 8.17 provides a brief summary of the narrative of each Grade 5 AE and FDA's assessment of the causality in greater detail.

Table 8-17: FDA Analysis of Fatal Treatment-Emergent AEs in the Tissue-Agnostic Safety Population

Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality	Included in USPI
(b) (6)	(b) (6) year-old (b) (6) with metastatic RET fusion-positive (b) (6) developed **Grade 5 sepsis** and **Grade 5 aspiration** one year after starting selpercatinib.	The history is limited, but the cause of death is most consistent with sepsis.	Yes
	(b) (6) year-old (b) (6) with metastatic RET fusion-positive (b) (6) developed dyspnea and hypoxia 1.5 months after starting selpercatinib. Pulmonary angiography showed disease progression with bilateral pulmonary embolism, treated with enoxaparin and steroids. (b) (6) died due **Grade 5 dyspnea**.	The history is most consistent with metastatic disease progression.	No
	(b) (6) year-old (b) (6) with metastatic RET fusion-positive (b) (6) developed recurrent hematemesis attributed to disease progression and was hospitalized. (b) (6) died one week later due to **Grade 5 neoplasm progression**.	The history is most consistent with metastatic disease progression.	No

Source: Clinical Study Report

Section 6 (Adverse Reactions) of product labeling includes safety data for the Overall Safety Population (n=796). Fatal adverse reactions, excluding those definitively attributable to progressive disease or extraneous cause, occurred in 24 (3%) patients and are included in product labeling. Fatal adverse reactions included sepsis (n = 6), respiratory failure (n = 5), hemorrhage (n = 4), pneumonia (n = 3), pneumonitis (n = 2), cardiac arrest (n=2), sudden death (n = 1), and cardiac failure (n = 1).

Serious Adverse Events

Data:
Table 8-18 summarizes TE-SAEs.

Table 8-18. Treatment Emergent Serious Adverse Events All Causality Occurring in ≥2 Patients in Tissue-Agnostic Safety Population or ≥2% Patients in Overall Safety Population Tissue-Agnostic and Overall Safety Populations

	Tissue-Agnostic Safety Population N = 45		Overall Safety Population N = 796	
	All Causality, n (%)	Related, n (%)	All Causality, n (%)	Related, n (%)
Patients with treatment-emergent SAEs	**18 (40.0)**	**3 (6.7)**	**353 (44.3)**	**87 (10.9)**
Abdominal pain	2 (4.4)	0	20 (2.5)	3 (0.4)
Nausea	2 (4.4)	0	7 (0.9)	2 (0.3)
Pyrexia	2 (4.4)	0	10 (1.3)	2 (0.3)
Vomiting	2 (4.4)	0	11 (1.4)	1 (0.1)
Hypersensitivity	1 (2.2)	1 (2.2)	16 (2.0)	16 (2.0)
Dyspnea	1 (2.2)	0	18 (2.3)	0
Hyponatremia	1 (2.2)	0	18 (2.3)	0
Pneumonia	0	0	33 (4.1)	0
Pleural effusion	0	0	24 (3.0)	5 (0.6)

Abbreviations: N = number of patients in the safety population; n = number of patients in the specific category; SAE = serious adverse event.

Notes:

- Adverse events are sorted in descending frequency based on the all-causality count in the **Tissue-Agnostic Safety Population**.

The component Preferred Terms comprising each composite term (*italicized*) are provided in Table APP.2.7.4.1.

Data cutoff dates: 24 Sep 2021 (**Tissue-Agnostic Safety Population**); 15 Jun 2021 (**Overall Safety Population**)

Source: Mod 2.7.4 SCS Table 2.7.4.11

The Applicant's Position:

The trends for serious TEAEs in the **Tissue-Agnostic Safety Population** are consistent with the **Overall Safety Population**, and the known safety profile of selpercatinib.

The FDA's Assessment:

FDA agrees with the Applicant's summary of treatment-emergent SAEs. There were no serious TEAEs that occurred in >2 patients in the Tissue-Agnostic Safety Population.

In the Overall Safety Population (n=796), SAEs occurred in 44% of patients who received selpercatinib. The most frequent serious adverse reactions (in ≥2% of patients) were pneumonia, pleural effusion, abdominal pain, diarrhea, hemorrhage, dyspnea, and hyponatremia.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 8-19 summarizes TEAEs leading to treatment discontinuation.

Table 8-19. Treatment-Emergent Adverse Events of any Grade Leading to Study Drug Discontinuation Occurring in ≥1 Patients in Tissue-Agnostic Safety Population, all Causality *RET*-Fusion Positive Safety Analysis Populations

	Tissue-Agnostic Safety Population N = 45		Overall Safety Population N = 796	
	All Causality, n (%)	Related, n (%)	All Causality, n (%)	Related, n (%)
Patients with TEAEs leading to drug discontinuation	**4 (8.9)**	**1 (2.2)**	**64 (8.0)**	**25 (3.1)**
Aspartate aminotransferase increased	1 (2.2)	1 (2.2)	4 (0.5)	3 (0.4)
Alanine aminotransferase increased	1 (2.2)	1 (2.2)	5 (0.6)	4 (0.5)
Blood bilirubin increased	1 (2.2)	1 (2.2)	3 (0.4)	2 (0.3)
Drug-induced liver injury	1 (2.2)	1 (2.2)	1 (0.1)	1 (0.1)
Aspiration	1 (2.2)	0	0	0
Dyspnea	1 (2.2)	0	2 (0.3)	0
Jaundice cholestatic	1 (2.2)	0	1 (0.1)	0
Neck pain	1 (2.2)	0	0	0

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the safety population; n = number of patients in the specific category; TEAE = treatment-emergent adverse event.
Notes:
Percentage is calculated based on the number of patients in the column heading as the denominator.
TEAEs are defined as adverse events that start on or after the first administration of selpercatinib.
Patients are counted once within each Preferred Term.
Reported adverse event terms were coded using MedDRA (version 21.0).
Adverse events are sorted in descending frequency based on all causality in the **Tissue-Agnostic Safety Population**.
All discontinuations are reported based on Preferred Terms, not composite terms.
Data cutoff dates: 24 Sep 2021 (**Tissue-Agnostic Safety Population**); 15 Jun 2021 (**Overall Safety Population**)
Source: Mod 2.7.4 SCS Table 2.7.4.14

The Applicant's Position:

Selpercatinib is well tolerated across indications, even in heavily pretreated individuals, and has low rates of discontinuations due to AEs.

The FDA's Assessment:

FDA agrees with the Applicant's summary of TEAEs leading to selpercatinib discontinuation. The percentage of patients requiring permanent discontinuation due to an adverse event was similar in the Overall Safety Population (8%) and the Tissue-Agnostic Safety Population (9%).

In the Tissue-Agnostic Safety Population, 4 patients required discontinuation due to an adverse event:

- Subject (b) (6) was a (b) (6) with metastatic *RET* fusion-positive (b) (6) who developed Grade 3 drug-induced liver dysfunction with increased AST, ALT and bilirubin four weeks after starting selpercatinib. (b) (6) was treated with IV fluids, antibiotics, and steroids. Selpercatinib was discontinued and the patient recovered.
- Subject (b) (6) was a (b) (6) with metastatic *RET* fusion-positive (b) (6) who developed Grade 3 cholestatic jaundice in the setting of progressive disease four months after starting selpercatinib. Selpercatinib was discontinued and the patient died 3 weeks later.
- Subject (b) (6) was an (b) (6) with metastatic *RET* fusion-positive (b) (6) developed Grade 5 sepsis and Grade 5 aspiration one year after starting selpercatinib. (b) (6) also had Grade 3 neck pain, worsened from baseline, and MRI showed arthritis. (b) (6) was treated with antibiotics and selpercatinib was discontinued. Despite treatment, the patient died 2 weeks after hospitalization.
- Subject (b) (6) was a (b) (6) with metastatic *RET* fusion-positive (b) (6) developed dyspnea and hypoxia 1.5 months after starting selpercatinib. Pulmonary angiography showed disease progression with bilateral pulmonary embolism, treated with enoxaparin and steroids. (b) (6) died due Grade 5 dyspnea (respiratory failure).

Dose Interruption/Reduction Due to Adverse Effects

Data:

Table 8-20 summarizes TEAEs leading to selpercatinib being withheld by the investigator.

Table 8-20. Treatment Emergent Adverse Events of any Grade leading to study drug Withheld Occurring in ≥2 Patients in Tissue-Agnostic Safety Population, all Causality Tissue-Agnostic and Overall Safety Populations

	Tissue-Agnostic Safety Population N = 45		Overall Safety Population N = 796	
	All Causality, n (%)	Related, n (%)	All Causality, n (%)	Related, n (%)
Patients with TEAEs leading to dose withheld	25 (55.6)	15 (33.3)	511 (64.2)	353 (44.3)

Aspartate aminotransferase increased	8 (17.8)	6 (13.3)	94 (11.8)	75 (9.4)
Alanine aminotransferase increased	7 (15.6)	6 (13.3)	85 (10.7)	79 (9.9)
Abdominal pain	4 (8.9)	0	28 (3.5)	14 (1.8)
Fatigue	3 (6.7)	3 (6.7)	31 (3.9)	22 (2.8)
Blood alkaline phosphate increased	3 (6.7)	1 (2.2)	12 (1.5)	5 (0.6)
Blood bilirubin increased	2 (4.4)	1 (2.2)	13 (1.6)	10 (1.3)
Hyponatremia	2 (4.4)	0	18 (2.3)	4 (0.5)
Nausea	2 (4.4)	0	15 (1.9)	5 (0.6)
Vomiting	2 (4.4)	0	17 (2.1)	5 (0.6)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the safety population; n = number of patients in the specific category; TEAE = treatment-emergent adverse event.
Notes:
Percentage is calculated based on the number of patients in the column heading as the denominator.
TEAEs are defined as adverse events that start on or after the first administration of selpercatinib.
Patients are counted once within each Preferred Term and within each type of dose modification.
Reported adverse event terms were coded using MedDRA (version 21.0).
Adverse events are sorted in descending frequency based on the dose withheld count in the **Tissue-Agnostic Safety Population**.
All dose modifications are reported based on Preferred Terms, not composite terms.
Data cutoff dates: 24 Sep 2021 (**Tissue-Agnostic Safety Population**); 15 Jun 2021 (**Overall Safety Population**)
Source: Mod 2.7.4 SCS Table 2.7.4.12

Table 8-21 summarizes TEAEs leading to selpercatinib dose reduction by the investigator.

Table 8-21. Treatment-Emergent Adverse Events of any Grade Leading to Dose Reduction Occurring in Patients in Tissue-Agnostic Safety Population, all Causality *RET*-Fusion Positive Safety Analysis Populations

	Tissue-Agnostic Safety Population N=45		Overall Safety Population N=796	
	All Causality, n (%)	**Related, n (%)**	**All Causality, n (%)**	**Related, n (%)**
Patients with TEAEs leading to dose reduction	**14 (31.1)**	**12 (26.7)**	**324 (40.7)**	**295 (37.1)**
Aspartate aminotransferase increased	7 (15.6)	6 (13.3)	57 (7.2)	52 (6.5)
Alanine aminotransferase increased	6 (13.3)	6 (13.3)	62 (7.8)	58 (7.3)
Fatigue	2 (4.4)	2 (4.4)	26 (3.3)	23 (2.9)
Blood alkaline phosphate increased	1 (2.2)	1 (2.2)	6 (0.8)	5 (0.6)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the safety population; n = number of patients in the specific category; TEAE = treatment-emergent adverse event.
Notes:
Percentage is calculated based on the number of patients in the column heading as the denominator.
TEAEs are defined as adverse events that start on or after the first administration of selpercatinib.
Patients are counted once within each Preferred Term and within each type of dose modification.
Reported adverse event terms were coded using MedDRA (version 21.0).
Adverse events are sorted in descending frequency based on the dose withheld count in the **Tissue-Agnostic Safety Population**.
All dose modifications are reported based on Preferred Terms, not composite terms.
Data cutoff dates: 24 Sep 2021 (**Tissue-Agnostic Safety Population**); 15 Jun 2021 (**Overall Safety Population**)
Source: Mod 2.7.4 SCS Table 2.7.4.13

The Applicant's Position:

In both the **Tissue-Agnostic Safety Population** and the **Overall Safety Population** the most frequent TEAEs that led to a dose being withheld or a dose reduction were *ALT increased* and *AST increased*.
Most TEAEs were managed with doses being withheld or reduced, allowing patients to continue with treatment.

The FDA's Assessment:
In the Overall Safety Population (n=796), **dosage interruptions** due to an adverse reaction occurred in 64% of patients who received selpercatinib. Adverse reactions requiring dosage interruption in ≥5% of patients included increased ALT, increased AST, diarrhea, and hypertension. Dose interruptions in the Tissue Agnostic Safety Population were slightly lower (56%), with the same most common TEAEs of increased AST and ALT.

In the Overall Safety Population (n=796), **dose reductions** due to an adverse reaction occurred in 41% of patients who received selpercatinib. Adverse reactions requiring dosage reductions in ≥2% of patients included increased ALT, increased AST, QT prolongation, fatigue, diarrhea, drug hypersensitivity, and edema. Dose reductions in the Tissue Agnostic Safety Population were slightly lower (31%), with the same most common TEAEs of increased AST and ALT.

Significant Adverse Events

Significant AEs are reported and described in SAEs preceding this section and Treatment-emergent AEs, Adverse Reactions following, and Section 8.2.5.1 AESIs.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Treatment Emergent Adverse Events and Adverse Reactions

Data:
Table 8-22 provides an overview of TEAEs.

Table 8-23 summarizes TEAEs in the **Tissue-Agnostic Safety Population** compared to the **Overall Safety Population**.
The most common TEAEs in the **Tissue-Agnostic Safety Population** were also among the most common in the **Overall Safety Population** and all occurred above 30% in that population. The most common Grade ≥3 TEAEs in the **Tissue-Agnostic Safety Population** were also among the most common in the **Overall Safety Population**, with the exception of blood alkaline phosphatase increased which occurred in 2% of patients in the **Overall Safety Population**.
The TEAEs which occurred at a rate of at least 5% higher in the **Tissue-Agnostic Safety Population** were (SCS Section 2.7.4.2.1.1.1):

ALT increased: 6.5% higher (any grade); 42.2% vs. 35.7%
abdominal pain: 6.4% higher (Grade ≥3); 8.9% vs. 2.5%
blood alkaline phosphatase increased: 9.0% higher (Grade ≥3); 11.1% vs. 2.1%, and
dermatitis acneiform: 5.9% higher (any grade); 8.9% vs. 3.0%.

Table 8-22. Summary of Treatment-Emergent Adverse Events Tissue-Agnostic and Overall Safety Populations

	Tissue-Agnostic Safety Population N=45	Overall Safety Population N=796
Any TEAE, n (%)	45 (100)	795 (99.9)
Related to selpercatinib	40 (88.9)	756 (95.0)
Grade ≥3 TEAE, n (%)	29 (64.4)	572 (71.9)
Related to selpercatinib	17 (37.8)	307 (38.6)
TE-SAE, n (%)	18 (40.0)	353 (44.3)
Related to selpercatinib	3 (6.7)	87 (10.9)
Fatal TEAE, n (%)	3 (6.7)	45 (5.7)
Related to selpercatinib	0	1 (0.1)
TEAE leading to permanent treatment discontinuation, n (%)	4 (8.9)	64 (8.0)
Related to selpercatinib	1 (2.2)	25 (3.1)

Abbreviations: N = number of patients in the safety population; n = number of patients in the specific category; TEAE = treatment-emergent adverse event; TE-SAE = treatment-emergent serious adverse event.
Data cutoff dates: 24 Sep 2021 (**Tissue-Agnostic Safety Population**); 15 Jun 2021 (**Overall Safety Population**)
Source: Mod 2.7.4 SCS Table 2.7.4.7

Table 8-23. Treatment-Emergent Adverse Events by Preferred Term and Aggregating Composite Term

Occurring in ≥15% Patients in the Tissue-Agnostic Safety Population, any Grade Tissue-Agnostic and Overall Safety Populations

	Tissue-Agnostic Safety Population N=45		Overall Safety Population N=796	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Patients with any selected TEAEs	45 (100.0)	29 (64.4)	795 (99.9)	572 (71.9)
Alanine aminotransferase increased	19 (42.2)	7 (15.6)	284 (35.7)	91 (11.4)
Aspartate aminotransferase increased	17 (37.8)	6 (13.3)	292 (36.7)	70 (8.8)
Dry mouth	15 (33.3)	0	344 (43.2)	0
Abdominal pain	15 (33.3)	4 (8.9)	268 (33.7)	20 (2.5)
Hypertension	14 (31.1)	10 (22.2)	326 (41.0)	157 (19.7)
Fatigue	13 (28.9))	3 (6.7)	365 (45.9)	25 (3.1)
Diarrhea	13 (28.9)	1 (2.2)	374 (47.0)	40 (5.0)
Edema	11 (24.4)	0	386 (48.5)	6 (0.8)
Rash	11 (24.4)	0	261 (32.8)	5 (0.6)
Nausea	10 (22.2)	2 (4.4)	248 (31.2)	9 (1.1)
Constipation	10 (22.2)	0	261 (32.8)	6 (0.8)
Blood alkaline phosphatase increased	8 (17.8)	5 (11.1)	116 (14.6)	17 (2.1)
Pyrexia	8 (17.8)	0	135 (17.0)	1 (0.1)
Insomnia	8 (17.8)	0	115 (14.4)	0
Vomiting	7 (15.6)	2 (4.4)	178 (22.4)	14 (1.8)
Electrocardiogram QT prolonged	7 (15.6)	1 (2.2)	168 (21.1)	38 (4.8)
Dyspnea	8 (17.8)	1 (2.2)	179 (22.5)	25 (3.1)
Blood creatinine increased	7 (15.6)	1 (2.2)	227 (28.5)	15 (1.9)
Headache	7 (15.6)	0	220 (27.6)	11 (1.4)
Back pain	7 (15.6)	0	153 (19.2)	12 (1.5)
Decreased appetite	7 (15.6)	0	150 (18.8)	3 (0.4)
Thrombocytopenia	7 (15.6)	0	123 (15.5)	24 (3.0)

Abbreviations: N = number of patients in the safety population; TEAE = treatment-emergent adverse event.
Notes:
Adverse events are sorted in descending frequency based on the all-causality count in the **Tissue-Agnostic Safety Population**.
The component Preferred Terms comprising each composite term (*italicized*) are provided in Table APP.2.7.4.1.
Data cutoff dates: 24 Sep 2021 (**Tissue-Agnostic Safety Population**); 15 Jun 2021 (**Overall Safety Population**)
Source: Mod 2.7.4 SCS Table 2.7.4.8

Identification of ADRs

In the original NDA, identification of ADRs for selpercatinib was based on the safety data from LIBRETTO-001. Events were classified as ADRs based on predefined core safety information screening criteria, biologic plausibility, and clinical importance. Inferential and descriptive analytical criteria were used for the initial screening of AE data. Medical judgment was the

determining factor, and prevailed over inferential and descriptive analytical criteria, when determining ADRs for inclusion in the product labeling during the original NDA submission. No new ADRs were identified for patients treated with selpercatinib in the Tissue-Agnostic Safety Population.

The Applicant's Position:

The frequency of any-grade TEAEs, TE-SAEs, TEAEs leading to permanent treatment discontinuation, and fatal TEAEs in the **Tissue-Agnostic** and **Overall Safety Populations** were comparable.
The most common TEAEs in the **Tissue-Agnostic Safety Population** were also among the most common in the **Overall Safety Population** and all occurred above 30% in that population. These TEAE differences were not considered to be clinically meaningful due to underlying comorbidities associated with study disease in patients contributing to higher incidence rate and severity of these TEAEs in the **Tissue-Agnostic Safety Population**.

The FDA's Assessment:
FDA agrees with the Applicant's Position that the most common TEAEs in the Tissue Agnostic Safety Population (n=45) were similar to those in the Overall Safety Population (n=796).

In the Tissue Agnostic Safety Population (n=45), all patients had at least one TEAE and 64% had a Grade 3 or higher TEAE.

The most common all grade TEAEs occurred in similar or lower frequencies in the Tissue Agnostic Safety Population compared to the Overall Safety Population. No all grade TEAE occurred with a >10% increased frequency in the Tissue Agnostic Safety Population compared to the Overall Safety Population.

The most common Grade 3 or greater TEAEs were generally similar between the two populations, except two TEAEs had a >5% higher frequency in the Tissue Agnostic Safety Population: abdominal pain (8.9% vs. 2.5%) and increased alkaline phosphatase (11.1% vs. 2.1%). The small patient numbers in the Tissue Agnostic Safety Population make it challenging to draw meaningful conclusions based on these minor differences in TEAE frequency.

Table 8.24, which is included in Section 6 (Adverse Reactions) of product labeling, summarizes the adverse reactions that occurred in ≥20% of patients in LIBRETTO-001 (n=796).

Table 8-24: Adverse Reactions (≥20%) in Patients Who Received RETEVMO in LIBRETTO-001

Adverse Reaction	RETEVMO (n = 796)	
	Grades 1-4# (%)	Grades 3-4 (%)
Gastrointestinal		
Diarrhea[1]	47	5*
Dry Mouth	43	0
Abdominal pain[2]	34	2.5*
Constipation	33	0.8*
Nausea	31	1.1*
Vomiting	22	1.8*
Vascular		
Hypertension	41	20
General		
Edema[3]	49	0.8*
Fatigue[4]	46	3.1*
Arthralgia	21	0.3*
Skin		
Rash[5]	33	0.6*
Nervous System		
Headache[6]	28	1.4*
Respiratory		
Cough[7]	24	0
Dyspnea[8]	22	3.1
Investigations		
Prolonged QT interval	21	4.8*
Blood and Lymphatic System		
Hemorrhage[9]	22	2.6

1 Diarrhea includes diarrhea, defecation urgency, frequent bowel movements, gastrointestinal hypermotility, anal incontinence.

2 Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness, epigastric discomfort, gastrointestinal pain.

3 Edema includes edema, edema peripheral, face edema, periorbital edema, eye edema, eyelid edema, orbital edema, localized edema, lymphedema, scrotal edema, peripheral swelling, scrotal swelling, swelling, swelling face, eye swelling, generalized edema, genital edema.

4 Fatigue includes fatigue, asthenia, malaise.

5 Rash includes rash, rash erythematous, rash macular, rash maculopapular, rash morbilliform, rash papular, rash pruritic, butterfly rash, exfoliative rash, rash follicular, rash generalized, rash vesicular.

6 Headache includes headache, sinus headache, tension headache.

[7] Includes cough, productive cough, upper airway cough syndrome.

[8] Includes dyspnea, dyspnea exertional, dyspnea at rest.

[9] Hemorrhage includes hemorrhage, epistaxis, hematuria, hemoptysis, contusion, rectal hemorrhage, vaginal hemorrhage, ecchymosis, hematochezia, petechiae, traumatic hematoma, anal hemorrhage, blood blister, blood urine present, cerebral hemorrhage, gastric hemorrhage, hemorrhage intracranial, hemorrhage subcutaneous, spontaneous hematoma, abdominal wall hematoma, angina bullosa hemorrhagica, conjunctival hemorrhage, disseminated intravascular coagulation, diverticulum intestinal hemorrhagic, eye hemorrhage, gastrointestinal hemorrhage, gingival bleeding, hematemesis, hemorrhagic stroke, hemorrhoidal hemorrhage, hepatic hemorrhage, hepatic hematoma, intraabdominal hemorrhage, laryngeal hemorrhage, lower gastrointestinal hemorrhage, melena, mouth hemorrhage, occult blood positive, post procedural hemorrhage, postmenopausal hemorrhage, pelvic hematoma, periorbital hematoma, periorbital hemorrhage, pharyngeal hemorrhage, pulmonary contusion, purpura, retinal hemorrhage, retroperitoneal hematoma, scleral hemorrhage, skin hemorrhage, subarachnoid hemorrhage, subdural hemorrhage, upper gastrointestinal hemorrhage, uterine hemorrhage, vessel puncture site hematoma.

* Only includes a grade 3 adverse reaction.

[#] Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03

Source: adae.xpt

Clinically relevant adverse reactions in ≤15% of patients who received RETEVMO include hypothyroidism (13%) and, hypersensitivity (6%); <2% of patients experienced interstitial lung disease/pneumonitis, chylothorax, chylous ascites, or tumor lysis syndrome.

Laboratory Findings

Data:
Analysis of postbaseline treatment-emergent laboratory abnormalities for serum hematology (including Grade ≥3 hematological laboratory data) and chemistry (including ALT and AST increased) are provided in Table 8-25 and Table 8-26, respectively.

Table 8-25. Treatment-Emergent Abnormal Hematologic Laboratory Tests Tissue-Agnostic and Overall Safety Populations

	N[a]	All Grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3/4 n (%)
Tissue-Agnostic Safety Population (Total=45)							
Lymphocyte count decreased	43	22 (51.2)	2 (4.7)	14 (32.6)	6 (14.0)	0	6 (14.0)
Hemoglobin decreased	45	11 (24.4)	3 (6.7)	6 (13.3)	2 (4.4)	0	2 (4.4)
Neutrophil count decreased	45	9 (20.0)	3 (6.7)	4 (8.9)	2 (4.4)	0	2 (4.4)
Platelets decreased	45	16 (35.6)	10 (22.2)	6 (13.3)	0	0	0
WBC count decreased	45	19 (42.2)	11 (24.4)	8 (17.8)	0	0	0
Overall Safety Population (Total=796)							
Lymphocyte count decreased	765	396 (51.8)	70 (9.2)	177 (23.1)	135 (17.6)	14 (1.8)	149 (19.5)
Hemoglobin decreased	791	225 (28.4)	125 (15.8)	72 (9.1)	28 (3.5)	0 (0.0)	28 (3.5)
Neutrophil count decreased	771	192 (24.9)	87 (11.3)	80 (10.4)	21 (2.7)	4 (0.5)	25 (3.2)
Platelets decreased	791	296 (37.4)	243 (30.7)	28 (3.5)	15 (1.9)	10 (1.3)	25 (3.2)
WBC count decreased	791	385 (48.7)	240 (30.3)	127 (16.1)	16 (2.0)	2 (0.3)	18 (2.3)

Abbreviations: N = number of patients in the safety population; n = number of patients in the specific category; WBC = white blood cell.

[a] Percentage is calculated based on the number of patients in the corresponding safety analysis set (N) with a baseline assessment and at least 1 postbaseline assessment as the denominator.

Data cutoff dates: 24 Sep 2021 (**Tissue-Agnostic Safety Population**); 15 Jun 2021 (**Overall Safety Population**)
Source: Mod 2.7.4 SCS Table 2.7.4.21

Table 8-26. Treatment-Emergent Abnormal Serum Chemistry Tests Tissue-Agnostic and Overall Safety Populations

	N[a]	All Grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3/4 n (%)
Tissue-Agnostic Safety Population (Total=45)							
Aspartate aminotransferase increased	45	27 (60.0)	9 (20.0)	10 (22.2)	8 (17.8)	0	8 (17.8)
Calcium decreased	45	17 (37.8)	10 (22.2)	6 (13.3)	0	1 (2.2)	1 (2.2)
Albumin decreased	45	22 (48.9)	9 (20.0)	10 (22.2)	3 (6.7)	0	3 (6.7)
Alanine aminotransferase increased	45	25 (55.6)	8 (17.8)	10 (22.2)	7 (15.6)	0	7 (15.6)
Glucose increased	45	19 (42.2)	9 (20.0)	6 (13.3)	4 (8.9)	0	4 (8.9)
Creatinine increased[b]	45	9 (20.0)	7 (15.6)	2 (4.4)	0	0	0
Sodium decreased	45	21 (46.7)	17 (37.8)	0	3 (6.7)	1 (2.2)	4 (8.9)
Alkaline phosphatase increased	45	21 (46.7)	10 (22.2)	7 (15.6)	3 (6.7)	1 (2.2)	4 (8.9)
Total cholesterol increased	44	10 (22.7)	6 (13.6)	1 (2.3)	1 (2.3)	2 (4.5)	3 (6.8)
Potassium increased	45	8 (17.8)	5 (11.1)	3 (6.7)	0	0	0
Glucose decreased	45	8 (17.8)	5 (11.1)	3 (6.7)	0	0	0
Magnesium decreased	44	13 (29.5)	12 (27.3)	1 (2.3)	0	0	0
Total bilirubin increased	45	15 (33.3)	7 (15.6)	4 (8.9)	3 (6.7)	1 (2.2)	4 (8.9)
Phosphate decreased	44	10 (22.7)	2 (4.5)	6 (13.6)	2 (4.5)	0	2 (4.5)
Potassium decreased	45	7 (15.6)	5 (11.1)	0	1 (2.2)	1 (2.2)	2 (4.4)
Overall Safety Population (Total=796)							
Aspartate aminotransferase increased	791	466 (58.9)	317 (40.1)	65 (8.2)	77 (9.7)	7 (0.9)	84 (10.6)
Calcium decreased	791	464 (58.7)	255 (32.2)	164 (20.7)	34 (4.3)	11 (1.4)	45 (5.7)
Albumin decreased	790	440 (55.7)	256 (32.4)	166 (21.0)	18 (2.3)	0 (0.0)	18 (2.3)

	N[a]	All Grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3/4 n (%)
Alanine aminotransferase increased	791	439 (55.5)	276 (34.9)	70 (8.8)	85 (10.7)	8 (1.0)	93 (11.8)
Glucose increased	791	419 (53.0)	282 (35.7)	115 (14.5)	19 (2.4)	3 (0.4)	22 (2.8)
Creatinine increased[b]	791	374 (47.3)	148 (18.7)	207 (26.2)	12 (1.5)	7 (0.9)	19 (2.4)
Sodium decreased	791	329 (41.6)	239 (30.2)	0 (0.0)	82 (10.4)	8 (1.0)	90 (11.4)
Alkaline phosphatase increased	791	318 (40.2)	223 (28.2)	68 (8.6)	25 (3.2)	2 (0.3)	27 (3.4)
Total cholesterol increased	779	272 (34.9)	222 (28.5)	37 (4.7)	1 (0.1)	12 (1.5)	13 (1.7)
Potassium increased	791	272 (34.4)	184 (23.3)	67 (8.5)	17 (2.1)	4 (0.5)	21 (2.7)
Glucose decreased	791	267 (33.8)	195 (24.7)	64 (8.1)	6 (0.8)	2 (0.3)	8 (1.0)
Magnesium decreased	787	259 (32.9)	239 (30.4)	15 (1.9)	3 (0.4)	2 (0.3)	5 (0.6)
Total bilirubin increased	791	233 (29.5)	140 (17.7)	71 (9.0)	22 (2.8)	0 (0.0)	22 (2.8)
Phosphate decreased	785	154 (19.6)	29 (3.7)	98 (12.5)	26 (3.3)	1 (0.1)	27 (3.4)
Potassium decreased	791	151 (19.1)	137 (17.3)	0 (0.0)	11 (1.4)	3 (0.4)	14 (1.8)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; N = number of patients in the safety population; n = number of patients in the specific category.

[a] Percentage is calculated based on the number of patients in the corresponding safety analysis set (N) with baseline assessment and at least 1 postbaseline assessment as the denominator

[b] Toxicity grade assignment based on CTCAE (version 5.0).

Data cutoff dates: 24 Sep 2021 (**Tissue-Agnostic Safety Population**); 15 Jun 2021 (**Overall Safety Population)**
Source: Mod 2.7.4 SCS Table 2.7.4.22

The Applicant's Position:

The incidence of treatment-emergent hematology abnormalities in the **Tissue-Agnostic Safety Population** was similar to that of the **Overall Safety Population**.
There were no clinically meaningful differences in the incidence of treatment-emergent serum chemistry abnormalities in the **Tissue-Agnostic Safety Population** compared to the **Overall Safety Population**.
The Laboratory abnormalities frequently observed in the **Tissue-Agnostic Safety Population** and **Overall Safety Population** are consistent with the recognized ADRs for selpercatinib.

The FDA's Assessment:
FDA agrees with the Applicant's Position that the most common laboratory abnormalities in the Tissue Agnostic Safety Population (n=45) were similar to those in the Overall Safety Population (n=796).

No lab abnormality of all grades occurred with a >10% increased frequency in the Tissue Agnostic Safety Population compared to the Overall Safety Population.

The most common Grade 3 or greater lab abnormalities were generally similar between the two populations, except the following lab abnormalities had a >5% higher frequency in the Tissue Agnostic Safety Population: increased AST (17.8% vs. 10.6%), increased glucose (8.9% vs. 2.8%), increased alkaline phosphatase (8.9% vs. 3.4%), increased cholesterol (6.8% vs. 1.7%), and total bilirubin increased (8.9% vs. 2.8%). The small patient numbers in the Tissue Agnostic Safety Population make it challenging to draw meaningful conclusions based on these minor differences in lab abnormality frequency.

Table 8.27, which is included in Section 6 (Adverse Reactions) of product labeling, summarizes select laboratory abnormalities worsening from baseline that occurred in ≥20% of patients in LIBRETTO-001 (n=796).

Table 8-27: Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received RETEVMO in LIBRETTO-001

	RETEVMO[1]	
Laboratory Abnormality	**Grades 1-4[#] (%)**	**Grades 3-4 (%)**
Chemistry		
Increased AST	59	11
Decreased calcium	59	5.7
Increased ALT	56	12
Decreased albumin	56	2.3

Increased glucose	53	2.8
Increased creatinine	47	2.4
Decreased sodium	42	11
Increased alkaline phosphatase	40	3.4
Increased total cholesterol	35	1.7
Increased potassium	34	2.7
Decreased glucose	34	1.0
Decreased magnesium	33	0.6
Increased bilirubin	30	2.8
Hematology		
Decreased lymphocytes	52	20
Decreased platelets	37	3.2
Decreased hemoglobin	28	3.5
Decreased neutrophils	25	3.2

[1] Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 765 to 791 patients.

[#] Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03

Source: adlb.xpt

Vital Signs

Data:

Vital sign assessments included heart rate, respiration rate, temperature, body weight, and blood pressure. Abnormal findings in blood pressure are considered as AESI and are described in Section 8.2.5
For the other assessments, most patients in the **Tissue-Agnostic Safety Population** and **Overall Safety Population** maintained their baseline grades at the last postbaseline assessment

The Applicant's Position:
There were no significant new findings

The FDA's Assessment:
FDA agrees with the Applicant's position. In the Overall Safety Population (n=796), the median weight was 69.3 kilograms (range 26.8 to 197.3). The median heart rate was 79 beats per minute (range 32 to 222). Excluding the one patient with a heart rate value of 222, the upper limit was 143 beats per minute. The median respiratory rate was 17 breaths per minute (range 6 to 40). The median temperature 36.6 degrees Celsius (range 34.1 to 39.5). Twenty-four patients (3%) had temperature values > 38 degrees Celsius. The median systolic blood pressure

was 122 mmHg (range 68 to 218), and the median diastolic blood pressure was 76 mmHg (range 30 to 148). Hypertension is a known safety risk with selpercatinib and is included in the Warnings and Precautions section of product labeling.

Electrocardiograms (ECGs)

Data:

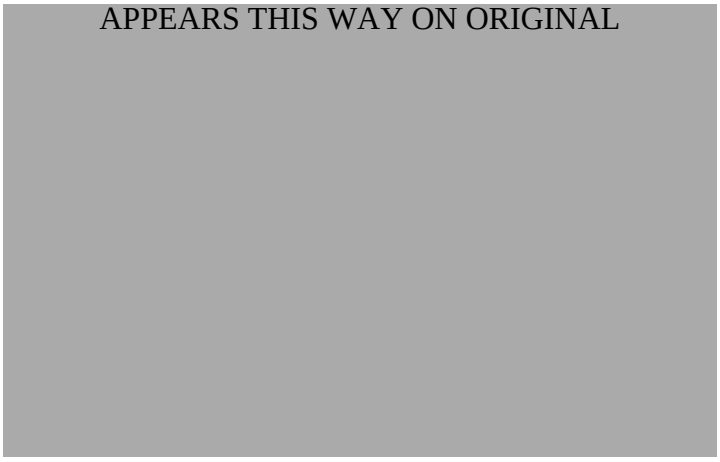


Table 8-28 outlines the ECG values. One patient (2.2%) in the **Tissue-Agnostic Safety Population** experienced an increase in QTcF of greater than 60 msec from baseline that was concurrent with the absolute QTcF greater than 500 msec.

APPEARS THIS WAY ON ORIGINAL

Table 8-28. 12-Lead Electrocardiogram Results Tissue-Agnostic and Overall Safety Populations

	Tissue-Agnostic Safety Population N = 45	Overall Safety Population N = 796
Absolute maximum postbaseline QTcF result, n (%)		
≤450	25 (55.6)	314 (39.6)
>450-480	16 (35.6)	325 (41.0)
>480-500	3 (6.7)	95 (12.0)
>500	1 (2.2)	58 (7.3)
Total	45 (100.0)	792 (100.0)
Patients[a]	45	792
Maximum QTcF result postbaseline[b], n (%)		
Increased >30 msec from baseline	31 (68.9)	569 (71.8)
Increased >60 msec from baseline	9 (20.0)	157 (19.8)
Last QTcF result postbaseline[b], n (%)		
Increased >30 msec from baseline	12 (26.7)	186 (23.5)
Increased >60 msec from baseline	1 (2.2)	17 (2.1)

Abbreviations: ECG = electrocardiogram; N = number of patients in the safety population; n = number of patients in the specific category; QTcF = QT interval corrected for heart rate using Fridericia's formula.

[a] Patients with both baseline and postbaseline ECGs.

[b] Patients may be counted in more than 1 row.

Notes:

Percentages are based on the number of patients (n) with a baseline assessment and at least 1 postbaseline assessment in the corresponding safety analysis set as the denominator.

Baseline is defined as the last measurement available prior to the first dose of selpercatinib.

Data cutoff dates: 24 Sep 2021 (**Tissue-Agnostic Safety Population**); 15 Jun 2021 (**Overall Safety Population**)
Source: Mod 2.7.4 SCS Table 2.7.4.23

The Applicant's Position:

There were no significant new findings

The FDA's Assessment:

FDA agrees with the Applicant's position. Refer to the original review for FDA's in-depth analysis regarding QT prolonging potential of selpercatinib. The dedicated QT review found that concentration-dependent QTc prolongation was detected in the thorough QT study.

In the Tissue Agnostic Safety Population (n=45), 7 patients (16%) had any grade TEAE of prolonged QTc interval and 1 patient (2.2%) had a Grade 3 TEAE.

In the updated Overall Safety Population (n=796), 21% of patients had any grade TEAE of prolonged QTc interval and 4.8% of patients had Grade 3 TEAEs.

There were no Grade 4 or 5 events of prolonged QTc or Torsades de Pointes. QT Interval Prolongation is included in the Warnings and Precautions section of product labeling, and dose modification recommendations for prolonged QTc are included in Section 2 of product labeling.

QT

Not applicable

The FDA's Assessment:
Refer to ECG section above.

Immunogenicity

Not applicable

The FDA's Assessment:
No safety issues related to immunogenicity were identified for selpercatinib.

Analysis of Submission-Specific Safety Issues

8.2.5.1 Adverse Events of Special Interest

Data:
Table 8-29 outlines the frequency of AEs of special Interest.

Table 8-29. Frequency of Adverse Events of Special Interest

	Any Grade (%)		Grade 3 or greater (%)	
	Tissue-Agnostic Safety Population	**Overall Safety Population**	**Tissue-Agnostic Safety Population**	**Overall Safety Population**
Liver Injury				
AST Increased	37.8	36.7	13.3	8.8
ALT Increased	42.2	35.7	15.6	11.5
Hypertension	31.1	41.0	22.2	19.7
Hypersensitivity	2.2	5.9	0.0	1.9
ECG QT Prolongation	15.6	21.1	2.2	4.8

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase.
Source: Mod 2.5 CO Table 2.5.5.1

The Applicant's Position:

The AESI observed are monitorable and manageable with successful dose-modification strategies, which allow most patients who experience these events to continue therapy.

The FDA's Assessment:
Refer to the Clinical and Statistical Review of selpercatinib sNDA 213246 Supplement 7 for a full review of the Adverse Events of Special Interest in the Overall Safety Population (n=796).

There were no unique AESI's identified in the Tissue Agnostic Safety Population during the review.

Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable

The FDA's Assessment:
Not applicable

Safety Analyses by Demographic Subgroups

The Applicant's Position:

Supportive analyses were performed to assess the safety and tolerability of selpercatinib across selected subgroups and special populations. Although numerical differences are noted in the subpopulations of the **Tissue-Agnostic Safety Population**, given the limited number of patients in each subgroup, these differences are not considered to be clinically significant.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Specific Safety Studies/Clinical Trials

No specific studies were conducted to evaluate safety concerns

The FDA's Assessment:
Not applicable

Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

Not applicable

The FDA's Assessment:
FDA agrees. No new information related to human carcinogenicity is provided in the current submission.

Human Reproduction and Pregnancy

The Applicant's Position:

As of the sNDA data cutoff, there has been no exposure to selpercatinib during pregnancy or lactation.
Preclinical data in animals suggest risk of fetal harm when administered during pregnancy; therefore, women who were known to be pregnant were excluded from the study; women of childbearing potential and men were required to use highly effective contraception during participation in any clinical study. Therefore, no human data are available.
There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, women are advised not to breastfeed during selpercatinib treatment, and if known to be breast-feeding, were excluded from the study.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Pediatrics and Assessment of Effects on Growth
Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable

The FDA's Assessment:
FDA agrees with the Applicant's position that no new information regarding pediatric data is provided in the current submission.

The review team notes that the safety and effectiveness of selpercatinib have been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced RET fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate). Use of selpercatinib for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older. The safety and effectiveness of selpercatinib have not been established in these indications in patients less than 12 years of age. Refer to the original multidisciplinary review dated May 8, 2020 for additional details.

Non-clinical studies identified concern for increased physeal thickness of multiple bones, extending into the metaphysis and associated with decreased trabecular bone, which was partially reversible at doses approximately equivalent to or greater than the adult human exposure at the clinical dose of 160 mg twice daily. Growth plate changes were associated with impairment of bone remodeling, resulting in decreased femur length and with reduction in bone mineral density. The product labeling recommends monitoring growth plates in adolescent patients with open growth plates and considering interrupting or discontinuing therapy based on the severity of any growth plate abnormalities and based on an individual risk-benefit assessment.

Postmarketing Requirement (PMR) 3829-4 from the original accelerated approval includes the following:

> Submit the final report, of an integrated safety analysis from clinical studies that further characterize the potential serious risk of long-term adverse effects of selpercatinib on growth and development, including an assessment of growth plate abnormalities in a sufficient number of adolescent patients 12 years of age and older with RET mutant MTC and RET fusion-positive thyroid cancer. Patients will be monitored for growth and development using age-appropriate screening tools. Evaluations will include growth as measured by height, weight, height velocity and height standard deviation scores, age at adrenarche if applicable (males), age at menarche if applicable (females) and Tanner stage. Patient monitoring will be performed until discontinuation of study treatment or a minimum of 5 years from start of treatment, whichever occurs first. Include the datasets with the final report. The results from this report may inform labeling.
>
> The timetable for this PMR is as follows:
>
> Trial Completion: 06/2025
> Final Report Submission: 12/2025

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

Overdose

No overdoses, defined as a daily exposure that exceeded the maximum daily assigned dose of 320 mg, 400 mg, or 480 mg (dependent on assignment of 160 mg BID, 200 mg BID, or 240 mg BID, respectively), have occurred as of the 24 September 2021 data cutoff in the selpercatinib program.

As of the 24 September 2021 data cutoff, no known antidote exists for selpercatinib overdose. Standard supportive measures were to be followed in the event of an acute overdose. No evidence exists to date of adverse cumulative effects with long-term chronic dosing with selpercatinib.

Drug Abuse

No information is available at this time on selpercatinib abuse or misuse, nor is there evidence that selpercatinib would be a candidate for such.

Withdrawal and rebound

No studies or analyses specifically addressed clinical issues related to selpercatinib withdrawal or rebound.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

Selpercatinib was first authorized on 08 May 2020 and has been granted marketing authorization in 36 countries. Selpercatinib is currently authorized for

RET fusion-positive NSCLC
RET fusion-positive TC, and
RET-mutant MTC.

Specific patient populations and dosing guidance vary by country. Cumulatively, up to 08 November 2021, an estimated 1000 patients were exposed to selpercatinib worldwide. The data reported from the post-marketing setting are generally consistent with the known safety profile of selpercatinib. Most events were reported as non-serious, and the most frequently reported events were recognised ADRs for selpercatinib or clinically expected in the target indication.

The Applicant's Position:

Overall, no new significant safety information has been identified from post-marketing sources. Most events were reported as nonserious, and the most frequently reported events were recognized ADRs for selpercatinib or clinically expected in the target indication.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Expectations on Safety in the Postmarket Setting

Not applicable

The FDA's Assessment:
Selpercatinib is expected to be administered by oncologists; management of and monitoring for adverse effects of anti-cancer medications including potentially serious adverse effects is standard practice in oncology. FDA does not anticipate that the safety of this product will differ significantly in the post-market setting.

Integrated Assessment of Safety

Not applicable

The FDA's Assessment:
The Overall Safety Population included 796 patients treated with selpercatinib in Study LIBRETTO-001. Overall, the adverse events observed are generally consistent with the current product labeling and there were no significant differences identified for the 45 patients in the Tissue Agnostic Safety Population.

In the Overall Safety Population, the most common (≥25%) treatment-emergent adverse events (TEAEs) were edema, diarrhea, fatigue, dry mouth, hypertension, abdominal pain, constipation, rash, nausea, and headache. The most common (≥5%) Grade 3 or 4 laboratory abnormalities (≥2%) were decreased lymphocytes, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), decreased sodium, and decreased calcium.

The review team considered that the safety profile of selpercatinib was acceptable when assessed in the context of a life-threatening disease. In addition, although selpercatinib can cause serious and severe toxicities, the safety concerns are described in product labeling; selpercatinib will be prescribed by oncologists who are trained to monitor and treat serious treatment-related toxicities. There were no significant safety concerns identified during the sNDA review requiring additional risk management tools such as a Risk Evaluation and Mitigation Strategy (REMS).

Refer to the original multidisciplinary review (May 8, 2022) and the review for supplement 7 (September 22, 2022) for a complete review of the original and updated safety database and a discussion of changes to Sections 5 and 6 of the product labeling.

SUMMARY AND CONCLUSIONS

Statistical Issues

The FDA's Assessment:
There are no major statistical issues in this application. The primary endpoint, ORR, was assessed using RECIST 1.1 by independent radiologic review. Secondary endpoints of PFS and OS were considered descriptive as time-to-events endpoints are not interpretable in a single-arm study.

For some of the tumor types included in the tissue agnostic analysis set, there are only 1 or 2 patients . Extrapolation of efficacy of selpercatinib to these less represented cancer types should be based on the clinical justification, biological rationale, and extent to which these cancer types can be considered as similar based on tumors harboring a *RET*-fusion genetic alteration.

Conclusions and Recommendations

The FDA's Assessment:
The recommendation for accelerated approval of selpercatinib for the treatment of adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options is based on Study LOXO-RET-17001 (LIBRETTO-001), an international, single-arm, dose-escalation and expansion study of selpercatinib in patients with advanced solid tumors including *RET* fusion-positive NSCLC.

The analysis population included patients who demonstrated a protocol-defined *RET* fusion identified based on a CLIA-certified (or equivalent) test with measurable disease per RECIST version 1.1, and received one or more doses of selpercatinib. The primary efficacy population included 41 patients with 14 different tumor types other than NSCLC and thyroid cancer, including the following tumor types: pancreatic adenocarcinoma, colorectal, salivary gland, unknown primary, breast, sarcoma, xanthogranuloma, carcinoid (bronchial), ovarian, small intestine, cholangiocarcinoma, pulmonary carcinosarcoma, rectal neuroendocrine and carcinoma of the skin.

There are no *RET*-directed therapies which have received regular approval for patients with *RET* fusion-positive solid tumors, and these patients are typically treated with the standard of care utilized for the given tumor type without a known oncogenic driver alteration. Available therapies in the second line or later for each of these tumor types per NCCN guidelines are variable, but most are chemotherapy-based with response rates generally < 30%.

For the 41 patients in the primary efficacy population, the confirmed ORR per RECIST 1.1 as determined by BIRC was 44% (95% CI 28, 60) with median DOR 24.5 months (95% CI 9.2, NE). The observed proportion of patients remaining in response per BIRC was 67% (95% CI 41, 87) at 6 months and 56% (95% 31, 56) at 12 months, respectively. Patients with 10 of 14 tumor types with a variety of fusion partners had objective responses by BIRC, including patients with the following tumors: pancreatic, colorectal, salivary, unknown primary, breast, soft tissue sarcoma, bronchial carcinoid, ovarian, small intestine, and cholangiocarcinoma.

The primary safety population included 796 patients treated with selpercatinib in Study LIBRETTO-001. The most common (≥25%) treatment-emergent adverse events (TEAEs) were edema, diarrhea, fatigue, dry mouth, hypertension, abdominal pain, constipation, rash, nausea, and headache. The most common (≥5%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, increased ALT, increased AST, decreased sodium, and decreased calcium. No new safety signals were identified during this review.

This submitted evidence in this supplemental NDA meets the statutory evidentiary standard for accelerated approval. Given the rarity of *RET* fusion-positive solid tumors, the magnitude of response observed in patients with NSCLC and thyroid cancer, and the diversity of tumor types with accompanying standard of care therapies, a randomized trial was not considered feasible. The durable responses observed across multiple tumor types in Study LIBRETTO-001, in the setting of a genetically-based biologic rationale and the existing approvals in advanced *RET* fusion-positive NSCLC and thyroid cancer, provide evidence of a clinically meaningful benefit of selpercatinib in the rare, genetically defined subgroup of patients with locally advanced or metastatic solid tumors with a *RET* gene fusion.

There is some uncertainty regarding the magnitude of responses expected in extremely rare tumor types represented in the efficacy population and in tumor types not represented in the efficacy population. In addition, there is uncertainty as to why the response rate observed in patients with colorectal cancer is lower than other tumors. However, considering the lack of available treatment options for these patients, strength of the scientific evidence across other tumor types, and acceptable safety profile of selpercatinib in this setting, the totality of the evidence favors approval for a tissue agnostic indication. Data from additional patients with non-NSCLC, non-thyroid *RET* fusion-positive solid tumors will be submitted as a post-marketing requirement to verify clinical benefit across tumor types. Based on the favorable risk-benefit assessment for this population with a serious, life-threatening disease, accelerated approval is

recommended for the following indication:

> Selpercatinib (RETEVMO) is indicated for the treatment of adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.

The recommended dose is 160 mg orally twice daily for patients 50 kg or greater, and 120 mg twice daily for patients < 50 kg.

X	X
Primary Statistical Reviewer Michelle Marcovitz, PhD	Statistical Team Leader Anup Amatya, PhD
X	X
Primary Clinical Reviewer Elizabeth Duke, MD	Clinical Team Leader Diana Bradford, MD

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

FDA did not refer this application to an advisory committee as no significant efficacy or safety issues were identified during the review that required external input for the proposed indication.

10 Pediatrics

The Applicant's Position:
Selpercatinib was granted orphan drug designation for treatment of tissue-agnostic *RET* fusion-positive solid tumors on 19 May 2022 and is exempt from PREA requirements.

The FDA's Assessment:
FDA agrees with the Applicant's position.

11 Labeling Recommendations

Data:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
1. Indications and Usage	Added "1.4 Other RET Fusion-Positive Solid Tumors" to add an indication for the treatment of (b) (4) (b) (4)	For consistency with labeling practice, FDA revised text for indication statement: RETEVMO is indicated for the treatment of adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options. Indication statements for NSCLC, Medullary Thyroid Cancer, and Thyroid Cancer were revised to include qualifier of either RET gene fusion or RET mutation "as detected by an FDA approved test".
2.1 Patient Selection		Deletion of (b) (4) (b) (4) Replaced with Information on FDA-approved test(s) for the detection of RET gene fusions and RET gene mutations is available at: http://www.fda.gov/CompanionDiagnostics. An FDA-approved companion diagnostic test for the detection of RET gene fusions and RET gene mutations in plasma or in tumors other than NSCLC and thyroid cancer is not currently available.
14. Clinical Studies	14.4 Other RET Fusion-Positive Solid Tumors Added relevant clinical information for the population of patients with RET fusion-positive tumors other than NSCLC and thyroid cancer.	Minor revisions to text, all numbers verified for accuracy. For consistency with labeling practice, text regarding for (b) (4) (b) (4) was deleted.

The Applicant's Position:
The sponsor considers the proposed labelling recommendations to be appropriate.

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

The FDA's Assessment:

The proposed prescribing information has been edited in accordance with 21 Code of Federal Regulations (CFR) and final and draft labeling guidances to ensure the safe and effective use of selpercatinib. Note that revisions made as part of the approval of supplemental NDA #7 (approved simultaneously) are described in the clinical/statistical review for that supplement.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The risks of selpercatinib are acceptable in the indicated patient population with a serious and life-threatening condition; the safe use of selpercatinib can be adequately implemented in the post-marketing setting through product labeling. No additional risk management strategies are recommended.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The following post-marketing requirements and post-marketing commitment will be issued for this application:

PMR 4342-1:

Complete clinical trial(s) to obtain data on the clinical efficacy of selpercatinib through more precise estimation of the overall response rate and mature response duration per independent review assessment, in at least 60 patients with locally advanced or metastatic *RET*-fusion positive solid tumors other than non-small cell lung cancer and thyroid cancer, who have progressed on prior systemic treatment or have no satisfactory alternative treatment options. A sufficient number of patients with tumor types for which responses require additional characterization (e.g., colorectal cancer, esophagogastric cancer, and glioma) will be evaluated. Overall response rate and duration of response will be assessed by independent central review and all responding patients will be followed for at least 12 months following the onset of response or until disease progression or death or early treatment discontinuation, whichever comes first. Include available data regarding *RET* fusion partners and co-occurring genetic alterations for all patients.

Trial Completion:	06/2025
Final Report Submission:	12/2025

PMC 4342-2:

Commitment to support the availability of an in vitro diagnostic device that demonstrates the device is essential to the safe and effective use of selpercatinib for treatment of patients with RET fusion-positive solid tumors through an appropriate analytical and clinical validation study using clinical trial data.

Study Completion:	09/2023
Final Report Submission:	03/2024

14 Division Director (OCP)

X

Stacy Shord, Pharm.D., BCOP, FCCP

15 Division Director (OB)

X

Pallavi Mishra-Kalyani, PhD

16 Division Director (Clinical)

X

Harpreet Singh, MD

17 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

18 Appendices

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Financial Disclosure

The Applicant's Position:
Financial disclosure information has been provided for all principal investigators and sub-investigators who participated at sites that enrolled patients with RET fusion-positive tissue-agnostic solid tumors in the single study, LIBRETTO-001, included in the sNDA submission.

The FDA's Assessment:
Financial disclosure information was collected for the investigators and sub-investigators participating in LOXO-RET-17001 (LIBRETTO-001).

Covered Clinical Study (Name and/or Number): LOXO-RET-17001 (LIBRETTO-001)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 568		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 2		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Nonclinical Pharmacology/Toxicology

Not applicable

The FDA's Assessment:
Not applicable

OCP Appendices (Technical documents supporting OCP recommendations)

Population PK Analysis

19.4.1.1. Executive Summary

The FDA's Assessment:
The Applicant updated the selpercatinib population PK model with new PK data from Study LOXO-RET-17001 (data cut-off date: 03/30/202006/15/2021) and J2G-GH-JZJK (data cut-off date: 04/12/2021) and evaluated the impact of tumor type (NSCLC, MTC and others) as a covariate on PK of selpercatinib. PK parameters in the updated population PK model were similar to the previous model. Tumor type was not found to be a significant covariate in the model. The results of population PK analysis are acceptable.

19.4.1.2. PPK Assessment Summary

The Applicant's Position:

The human population PK model for selpercatinib developed for the NSCLC sNDA was updated using pooled PK data from the LIBRETTO-001 study (data cut-off date 15 June 2021) and China study J2G-GH-JZJK (data available up to 12 April 2021), tested tumor type as a covariate, and re-estimated previously identified covariate effects.

Tumor type was not found to be a significant covariate to any of the tested PK parameters.

There was a 18.4% (bootstrap 95%CI: 11.3%, 25.9%) increase in bioavailability for Asian subjects in addition to effects of dose on CL/F and allometric body weight scaling.

Simulation from the population PK model suggests

Steady-state AUC and C_{max} overlap considerably across all 3 tumor types (i.e., NSCLC, MTC, and tissue-agnostic solid tumors) as well as race (i.e., Japanese, Chinese, Asian, and non-Asian).

A weight-based dosing (120 mg BID for subjects <50 kg and 160 mg BID for subjects ≥50 kg) was likely to produce similar exposures for subjects below or above 50 kg of weight.

General Information		
Objectives of PPK Analysis		Characterize selpercatinib PK profile Update PPK model submitted for NSCLC sNDA 2021 using pooled PK data from the LIBRETTO-001 study (data cut-off date 15 June 2021) and China study J2G-GH-JZJK (data available up to 12 April 2021) Test tumor type as a covariate, and re-estimate previously identified covariate effects Predict individual exposure for E-R assessment
Studies Included		LIBRETTO-001 (LOXO-RET-17001) study (data cut-off date 15 June 2021) and China study J2G-GH-JZJK (data available up to 12 April 2021)
Dose(s) Included		20, 40, 60, 80, 120, 160, 200, 240 mg *(Table 19-2)*
Population Included		*Patients*
Population Characteristics (Table 19-1 and Table 19-2)	General	Age - median 58 yr (15-92) Weight -median 66.7kg (26.8-179.4) Male N= 436 (51.7%); Female N= 408 (48.3%) Caucasian N= 520 (61.6%) Black or African American N= 25 (3.0%) Asian N=260 (30.8%) American Indian/Alaskan Native N=2 (0.2%) Native Hawaiian or Other Pacific Islander N= 1 (0.1%) Other N=31 (3.7%) Mising information N=5 (0.6%)
	Organ Impairment	N/A
	Pediatrics (if any)	No patients less than 12 yr
No. of Patients, PK Samples, and BLQ		Total 844 patients with 8205 observations used in the PPK analysis. 155 (1.85%) post-dose BLQ data was excluded. A total of 8360 concentration observation records from 845 subjects were considered for the analysis. No records were removed due to high CWRES considerations. Not considering the first predose sample, there were 155 (1.85%) data records that were excluded due to the concentrations being below the lower limit of quantitation. This left 8205 observable concentration records from 844 subjects (Subject LOXO-RET-

		17001-[redacted] (b) (6) had no measurable postdose observation records and was thus excluded from the analysis)
Sampling Schedule	Rich Sampling	See below
	In ITT Population	LIBRETTO-001 (LOXO-RET-17001) Blood for plasma pharmacokinetic (PK) assessment was collected at up to 1 hour predose and at 1, 2, and 4 hours (±15 minutes) and 8 hours (±30 minutes) postdose on Cycle 1 Day 8 (C1D8). In some cases, blood was also collected for plasma PK assessment on C1D1, C3D1, C5D1, and Day 8 of a subject's new dose (if the subject was intrasubject dose escalated). Additional PK sampling was also performed in subjects when considered necessary by the Investigator to understand exposure in relation to possible safety or efficacy findings or if there was a change in the selpercatinib formulation being administered. Study J2G-GH-JZJK Serial blood samples for intensive PK monitoring were collected on C1D1 and C1D8 for a total of 12 subjects, and blood samples for PPK (predose samples on Day 1 of each cycle) were collected from all enrolled subjects
Covariates Evaluated	Static	Tumor type
	Time-varying	Exposure change over time was not observed when given the same dose. No time varying covariate was tested.

Final Model	**Summary**	**Acceptability [FDA's comments]**
Software and Version	NONMEM®; version 7.4.3 R (versions 3.6.3 and 4.0.3)	Acceptable
Model Structure	A 2 compartment disposition model with sequential zero- and first-order absorption was utilized for description of selpercatinib PPK. IIV terms were included on CL/F, Vc/F, ka, and Dur.	Acceptable
Model Parameter Estimates	Table 19-3	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	Overall, the parameters of the model, including the covariate effects, were estimated with reasonable precision. Random interindividual effects with mean 0 and variance ω^2 (ETA) shrinkages from the final PPK were <50%, with the exception of absorption parameters.	Acceptable
BLQ for Parameter Accuracy	155 (1.85%) post-dose BLQ data was excluded, parameter accuracy	Acceptable

	assessment for BLQ was not carried out.	
GOF, VPC	Figure 19-1 Figure 19-2 Figure 19-3 Figure 19-4	Acceptable
Significant Covariates and Clinical Relevance	*Tumor type was not found to be a significant covariate to any of the tested PK parameters*	Acceptable
Analysis Based on Simulation	Figure 19-5 Figure 19-6 Figure 19-7	Acceptable
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK	No change	N/A

Table 18-1 Summary of Baseline Demographic Data in the PPK Analysis: Continuous Variables

Covariate (Unit)	LOXO-RET-17001 (N=767)	J2G-GH-JZJK (N=77)	Overall (N=844)
Age (years)			
Mean	57.1	50.6	56.6
SD	14.1	12.9	14.1
Median	58.0	54.0	58.0
Range	15-92	19-72	15-92
N	767	77	844
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Body weight (kg)			
Mean	71.2	64.1	70.5
SD	19.7	13.6	19.4
Median	67.4	61.5	66.7
Range	26.8-179.4	42-108	26.8-179.4
N	767	77	844
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Body mass index (kg/m^2)			
Mean	25.0	23.1	24.8
SD	5.9	3.7	5.7
Median	23.9	22.7	23.7

Covariate (Unit)	LOXO-RET-17001 (N=767)	J2G-GH-JZJK (N=77)	Overall (N=844)
Range	11.6-59.1	16.1-36.3	11.6-59.1
N	746	77	823
Missing	21 (2.7%)	0 (0.0%)	21 (2.5%)
Body surface area (m^2)			
Mean	1.8	1.7	1.8
SD	0.3	0.2	0.3
Median	1.8	1.7	1.8
Range	1.1-2.8	1.4-2.3	1.1-2.8
N	746	77	823
Missing	21 (2.7%)	0 (0.0%)	21 (2.5%)
Creatinine clearance (mL/min)			
Mean	96.9	104.6	97.7
SD	38.7	36.0	38.5
Median	91.8	101.0	93.0
Range	20.7-311.1	31.2-281.1	20.7-311.1
N	728	77	805
Missing	39 (5.1%)	0 (0.0%)	39 (4.6%)
ALT (U/L)			
Mean	25.2	22.0	24.9
SD	18.6	14.8	18.3
Median	19.3	16.2	19.0
Range	4-158	4-80	4-158
N	728	77	805
Missing	39 (5.1%)	0 (0.0%)	39 (4.6%)
AST (U/L)			
Mean	27.2	25.2	27.0
SD	17.6	13.9	17.3
Median	23.0	21.0	23.0
Range	6-233	9.5-78	6-233
N	728	77	805
Missing	39 (5.1%)	0 (0.0%)	39 (4.6%)
Bilirubin (mg/dL)			
Mean	9.8	4.0	9.3
SD	5.7	2.2	5.7

Covariate (Unit)	LOXO-RET-17001 (N=767)	J2G-GH-JZJK (N=77)	Overall (N=844)
Median	8.6	3.5	8.6
Range	2.9-56.4	1.12-12.6	1.1-56.4
N	728	77	805
Missing	39 (5.1%)	0 (0.0%)	39 (4.6%)

Source: summarystat.R
Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; N=number of subjects; PPK=population pharmacokinetic(s); SD=standard deviation

Table 19-2. Summary of BaselineTable Demographic Data in the PPK Analysis: Categorical Variables

Covariate	Category	LOXO-RET-17001 (N=767)	J2G-GH-JZJK (N=77)	Overall (N=844)
Subject-specific categorical covariates				
Sex, N (%)	Male	392 (51.1)	44 (57.1)	436 (51.7)
	Female	375 (48.9)	33 (42.9)	408 (48.3)
Race, N (%)	Caucasian	520 (67.8)	0 (0)	520 (61.6)
	Black or African American	25 (3.3)	0 (0)	25 (3.0)
	Asian	183 (23.9)	77 (100)	260 (30.8)
	American Indian/Alaskan Native	2 (0.3)	0 (0)	2 (0.2)
	Native Hawaiian or Other Pacific Islander	1 (0.1)	0 (0)	1 (0.1)
	Other	31 (4.0)	0 (0)	31 (3.7)
	Missing	5 (0.7)	0 (0)	5 (0.6)
Japanese ethnicity, N (%)	No	690 (90)	77 (100)	767 (90.9)
	Yes	77 (10)	0 (0)	77 (9.1)
Chinese ethnicity, N (%)	No	767 (100)	0 (0)	767 (90.9)
	Yes	0 (0)	77 (100)	77 (9.1)
Asian ethnicity, N (%)	No	579 (75.5)	0 (0)	579 (68.6)
	Yes	183 (23.9)	77 (100)	260 (30.8)
	Missing	5 (0.7)	0 (0)	5 (0.6)
H2 receptor blocker, N (%)	No	517 (67.4)	76 (98.7)	593 (70.3)
	Yes	250 (32.6)	1 (1.3)	251 (29.7)
Proton pump inhibitor, N (%)	No	719 (93.7)	73 (94.8)	792 (93.8)
	Yes	48 (6.3)	4 (5.2)	52 (6.2)

Covariate	Category	LOXO-RET-17001 (N=767)	J2G-GH-JZJK (N=77)	Overall (N=844)
H2 receptor blocker or proton pump inhibitor, N (%)	No	501 (65.3)	72 (93.5)	573 (67.9)
	Yes	266 (34.7)	5 (6.5)	271 (32.1)
Weak CYP3A4 inhibitor, N (%)	No	614 (80.1)	77 (100)	691 (81.9)
	Yes	153 (19.9)	0 (0)	153 (18.1)
Moderate CYP3A4 inhibitor, N (%)	No	668 (87.1)	75 (97.4)	743 (88)
	Yes	99 (12.9)	2 (2.6)	101 (12)
Strong CYP3A4 inhibitor, N (%)	No	751 (97.9)	77 (100)	828 (98.1)
	Yes	16 (2.1)	0 (0)	16 (1.9)
Any CYP3A4 inhibitor, N (%)	No	539 (70.3)	75 (97.4)	614 (72.7)
	Yes	228 (29.7)	2 (2.6)	230 (27.3)
Weak CYP3A4 inducer, N (%)	No	767 (100)	77 (100)	844 (100)
	Yes	0 (0)	0 (0)	0 (0)
Moderate CYP3A4 inducer, N (%)	No	764 (99.6)	77 (100)	841 (99.6)
	Yes	3 (0.4)	0 (0)	3 (0.4)
Strong CYP3A4 inducer, N (%)	No	765 (99.7)	77 (100)	842 (99.8)
	Yes	2 (0.3)	0 (0)	2 (0.2)
Any CYP3A4 inducer, N (%)	No	762 (99.3)	77 (100)	839 (99.4)
	Yes	5 (0.7)	0 (0)	5 (0.6)
Tumor type, N (%)	RET mutant MTC	308 (40.2)	26 (33.8)	334 (39.6)
	RET fusion NSCLC	348 (45.4)	26 (33.8)	374 (44.3)
	Other[b]	111 (14.5)	25 (32.5)	136 (16.1)
Subject nonspecific categorical covariates				
Dose[a] (mg)	20	19 (2.0%)	0 (0%)	19 (1.8%)
	40	33 (3.5%)	12 (9.4%)	45 (4.2%)
	60	36 (3.9%)	0 (0%)	36 (3.4%)
	80	71 (7.6%)	18 (14.1%)	89 (8.4%)
	120	41 (4.4%)	21 (16.4%)	62 (5.8%)
	160	724 (77.6%)	77 (60.2%)	801 (75.5%)
	200	3 (0.3%)	0 (0%)	3 (0.3%)
	240	6 (0.6%)	0 (0%)	6 (0.6%)

Source: summarystat.R

[a] The percentage of subjects does not add to 100% because a subject may have received selpercatinib at more than 1 dose level during the study.

Abbreviations: CYP3A4=cytochrome P450 3A4; H2=Histamine-2; N=number of subjects; MTC=medullary thyroid cancer; NSCLC=non-small cell lung cancer; PPK=population pharmacokinetic(s); RET=rearranged during transfection

[b] The "Other" category includes 37 subjects who have tissue agnostic tumors

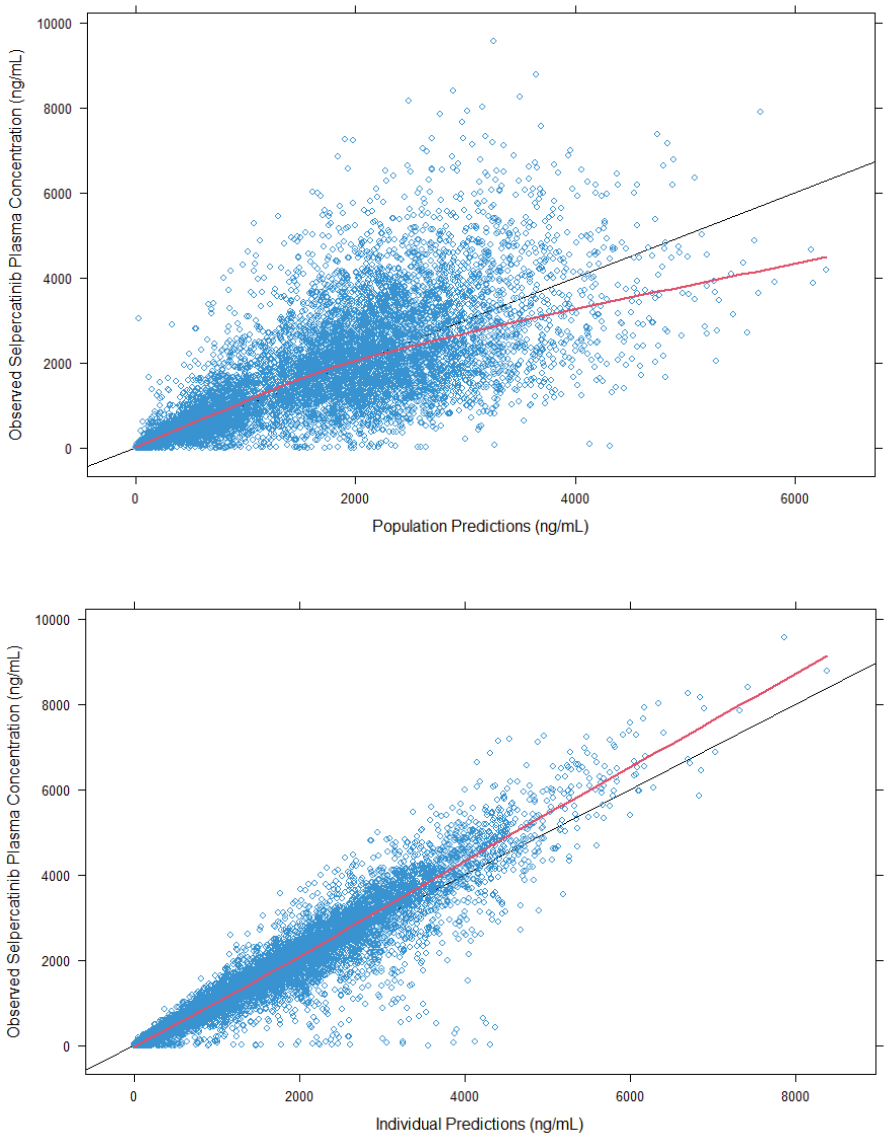
Table 19-3. Parameters of the Final Population PK Model (cupallo11u21)

	Estimate		Interindividual Variability		
Parameter (Unit)	**Typical Value**	**Bootstrap Final Model Median (2.5^{th}, 97.5^{th} Percentiles)**	**Typical Value**	**Bootstrap Final Model Median (2.5^{th}, 97.5^{th} Percentiles)**	**Shrinkage[a]**
CL/F (L/h)	6.03	6.03 (5.8, 6.3)	47.01%	47.0% (43.8%, 50.1%)	3.7%
Effect of dose on CL/F (%/mg)[c]	-0.3%	-0.3% (-0.4%, -0.02%)	–		–
Effect of Asian race on F_{rel} (%)[c]	18.4%	18.5% (11.3%, 25.9%)	–		–
Q/F (L/h)	30.5	30.8 (25.8, 37.2)	–		–
Vc/F (L)	102	100.7 (83.5, 112.6)	68.04%	68.2% (57.7%, 80.8%)	33.8%
Vp/F (L)	93.5	94.4 (85.8, 106.9)	–		–
ka (1/h)	1.42	1.39 (1.13, 1.62)	75.43%	74.2% (37.7%, 99.6%)	54.5%
Dur (h)	1.1	1.09 (1.02, 1.17)	57.1%	56.6% (49.0%, 63.3%)	52.3%
Residual variability					
Proportional residual error	25.9%	25.9% (23.9%, 27.9%)	–	–	8.5%
Additive residual error SD (ng/mL)	54.5	54.7 (40.1, 82.5)	–	–	8.5%

Source: cupallo11u21.lst and bootstrap_results.csv

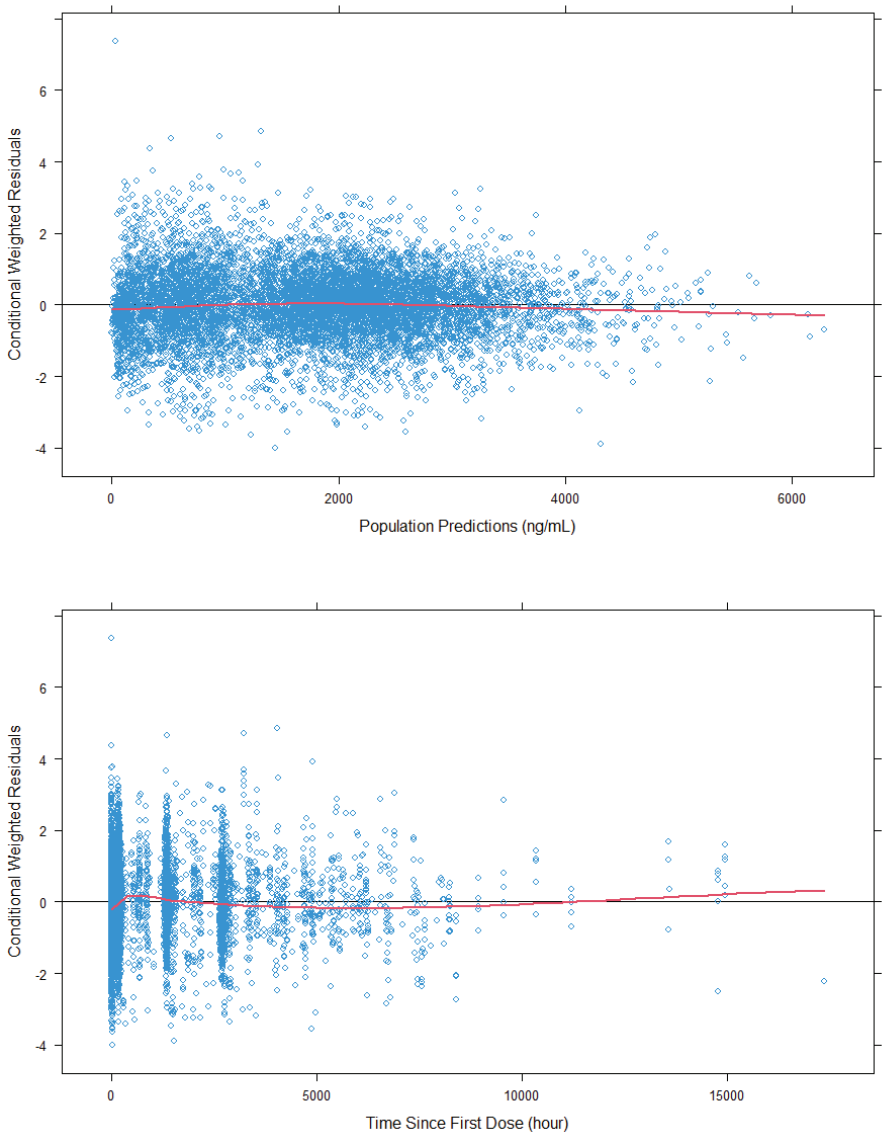
[a] Shrinkage (%) was calculated as 100×(1−SD of post hoc/estimated variance).

Abbreviations: CL/F=apparent clearance; F_{rel}=relative bioavailability; Dur=duration of zero-order absorption; IIV=interindividual variability; ka=absorption rate constant; PK=pharmacokinetic; Q/F=apparent distributional clearance; SD=standard deviation; Vc/F=apparent central volume of distribution; Vp/F=apparent peripheral volume of distribution



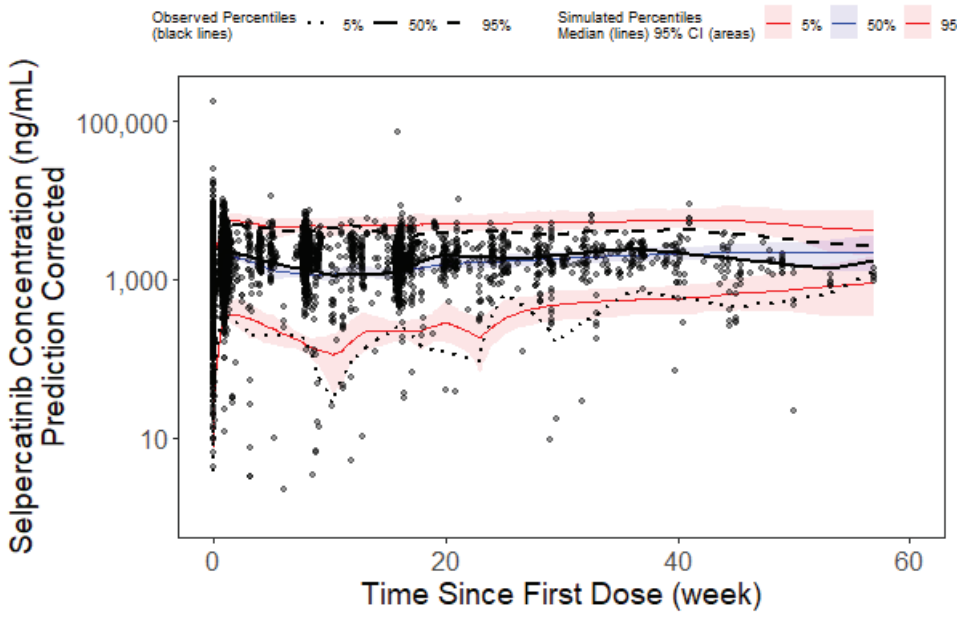
Source: summarystat.R
Note: Black line is the identity line. Red line is the LOESS.
Abbreviations: LOESS=locally estimated scatterplot smoothing; PPK=population pharmacokinetic(s)

Figure 19-1. Goodness of Fit Plots for Selpercatinib From the Final PPK Model



Source: summarystat.R
Note: Black line is the zero line. Red line is the LOESS.
Abbreviations: LOESS=locally estimated scatterplot smoothing; PPK=population pharmacokinetic

Figure 19-2. Residual Goodness-of-Fit Plots for Selpercatinib From the PPK Model



Source: ELIL-PMX-SELPERCATINIB-3499_POPPK_VPC.Rmd
Note: The solid line represents the median of the observed data. Shaded regions encompass 90% of the simulated (N=1000) values of the predicted medians and the 5th and 95th percentiles. Data points represent the prediction-corrected observed data.
Abbreviations: N=number of simulations; pcVPC=prediction-corrected visual predictive check; PPK=population pharmacokinetic(s)

Figure 19-3. pcVPC for the Final PPK on the Logarithmic Scale

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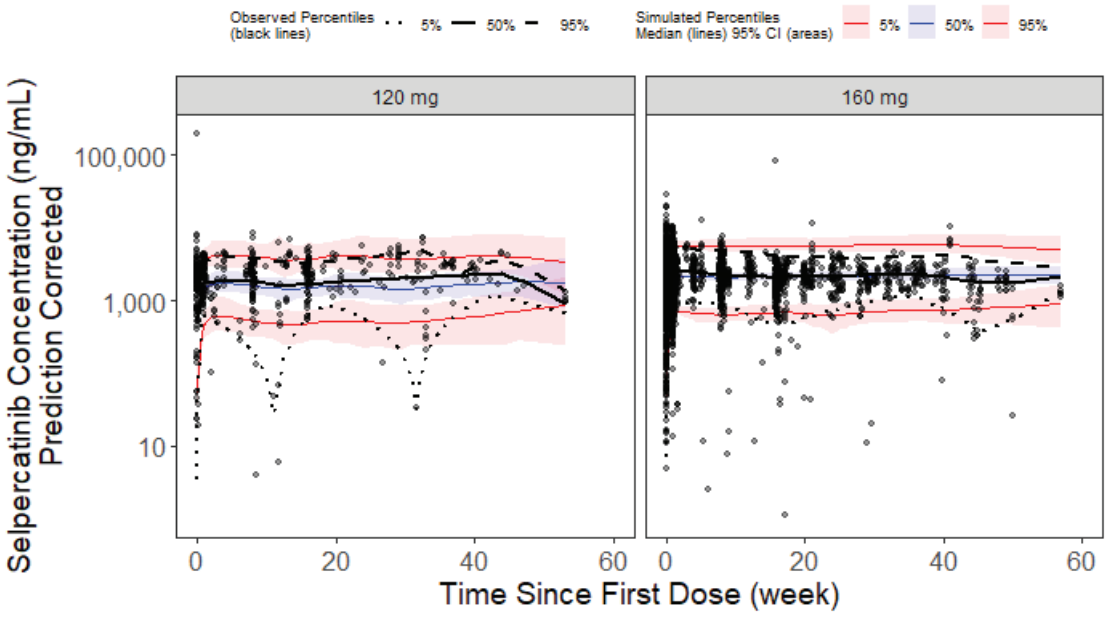

Source: ELIL-PMX-SELPERCATINIB-3499_POPPK_VPC.Rmd
Note: The solid line represents the median of the observed data. Shaded regions encompass 90% of the simulated (N=1000) values of the predicted medians and the 5th and 95th percentiles. Data points represent the prediction-corrected observed data.
Abbreviations: N=number of simulations; pcVPC=prediction-corrected visual predictive check; PPK=population pharmacokinetic(s)

Figure 19-4. pcVPC for the Final PPK Model Stratified by Dose on the Logarithmic Scale

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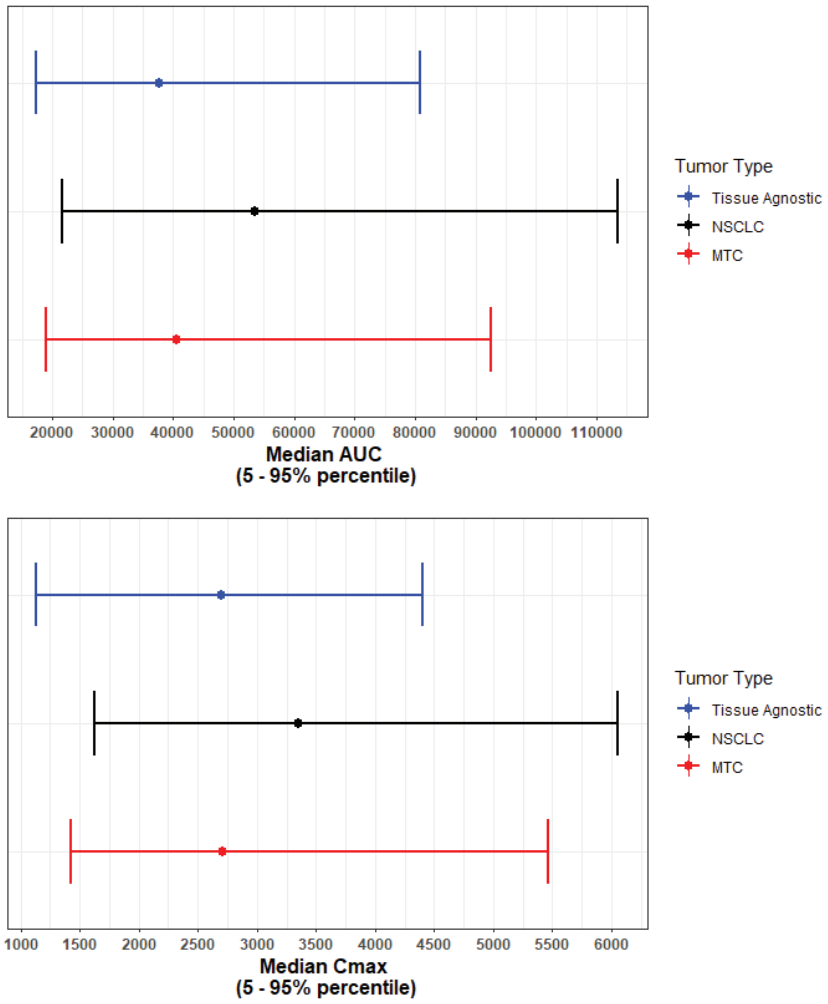

Source: ELIL-PMX-SELPERCATINIB-3499-simulation_forest_plots_03-03-22.Rmd
Abbreviations: AUC= area under the plasma concentration-time curve; Cmax=maximum selpercatinib concentration; MTC=medullary thyroid cancer; NSCLC=non-small cell lung cancer

Figure 19-5. Simulated Steady-State AUC and Cmax by Tumor Type

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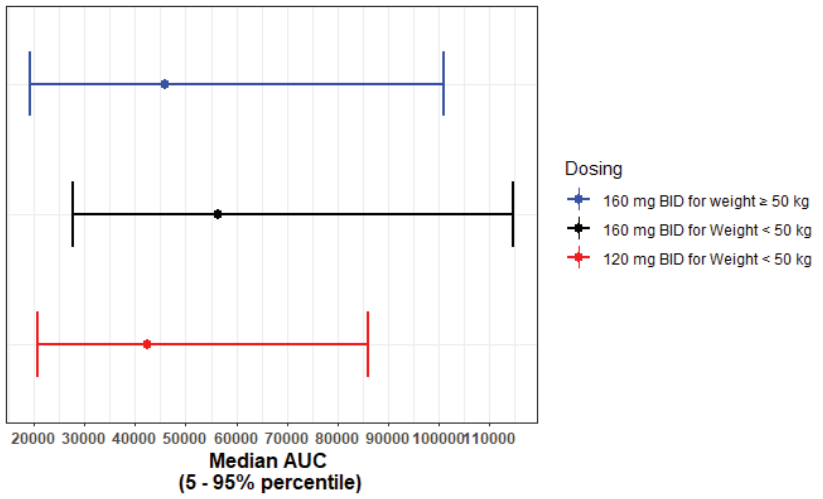

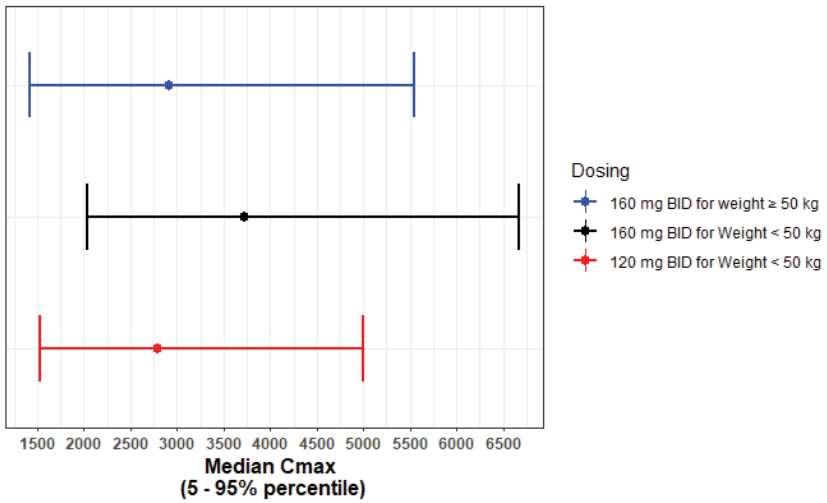

Source: ELIL-PMX-SELPERCATINIB-3499-simulation_forest_plots_03-03-22.Rmd
Abbreviations: AUC= area under the plasma concentration-time curve; Cmax=maximum selpercatinib concentration

Figure 19-6. Simulated Steady-State AUC and Cmax by Weight and Dosing

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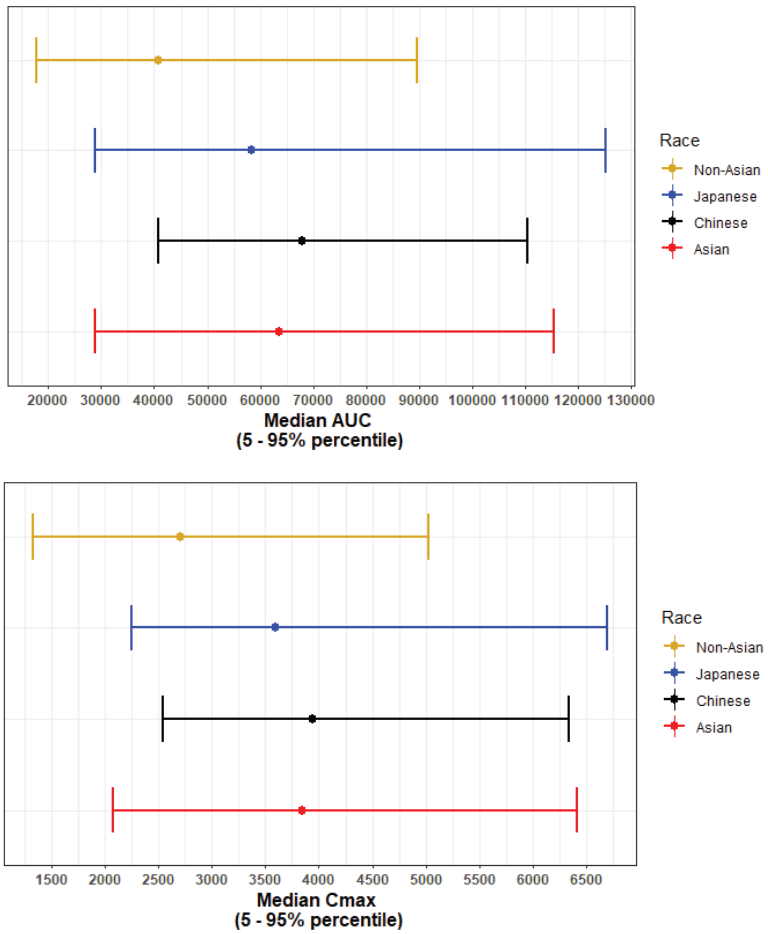


Source: ELIL-PMX-SELPERCATINIB-3499-simulation_forest_plots_03-03-22.Rmd
Abbreviations: AUC=area under the plasma concentration-time curve; Cmax=maximum selpercatinib concentration

Figure 19-7. Simulated Steady-State AUC and Cmax by Race

The FDA's Assessment:

The updated final population PK model appears to be reasonable due to the acceptable agreement between model prediction and observation. The estimation result is similar to the previous population PK model. Tumor type was not identified as a significant covariate on the tested PK parameters. Comparisons of AUCss and Cmax,ss by tumor type when all subjects received 160 mg BID are shown in **Figure 19-5**, **Table 19-4**, and **Table 19-5**. The significant overlap in exposure metrics across all 3 tumor types suggests selpercatinib exposure is similar across different tumor types.

Table 19-4: Summary of simulated AUCss by Tumor Type

	Geometric Mean	%CV	5th Percentile	95th Percentile	N
160 mg BID flat dose					
MTC	41144	59.3	19043	92545	334
NSCLC	51228	51.4	21623	113551	374
Tissue agnostic	37751	49.6	17409	80883	37
Other	49341	53.2	22514	106850	99
160 mg / 120 mg BID weight-based dose					
MTC	39913	58.9	17603	88907	334
NSCLC	49676	52.4	21145	104954	374
Tissue agnostic	35751	53.0	17409	80883	37
Other	47928	47.1	22514	98767	99

Source: LOXO-292-DMPK-050 02 LEGACY REPORT JZJA AND JZJK, Page 49, Table 15

Table 19-5: Summary of Simulated $C_{max,ss}$ by Tumor Type

	Geometric Mean	%CV	5th Percentile	95th Percentile	N
160 mg BID flat dose					
MTC	2736	45.4	1425	5464	334
NSCLC	3233	40.5	1628	6056	374
Tissue agnostic	2527	39.7	1135	4400	37
Other	3038	43.5	1716	5949	99
160 mg / 120 mg BID weight-based dose					
MTC	2654	44.3	1425	4986	334
NSCLC	3135	41.1	1558	5828	374
Tissue agnostic	2393	41.7	1135	4400	37
Other	2951	37.7	1716	5250	99

Source: LOXO-292-DMPK-050 02 LEGACY REPORT JZJA AND JZJK, Page 51, Table 18

19.4.1.3. PPK Review Issues

N/A

19.4.1.4. Reviewer's Independent Analysis

N/A

Exposure-Response Analysis

19.4.2.1. ER (efficacy) Executive Summary

The FDA's Assessment:

The applicant evaluated exposure efficacy relationships in the tissue-agnostic set of subjects (i.e., patients with *RET* fusion-positive tumors other than NSCLC and thyroid cancer) from LIBRETTO-001. No statistically significant ER relationship was identified. Due to the small sample size of the analysis, the result of the ER analysis is inconclusive.

19.4.2.2. ER (efficacy) Assessment Summary

The Applicant's Position:

The efficacy exposure-response analysis examined the overall response rate (ORR) in patients with tissue-agnostic solid tumors from the LIBRETTO-001 study (15 June 2021 cut-off date). A subject with a partial response or a complete response was labeled as a responder. No statistically significant predictor ($p < 0.05$) was identified in patients with tissue-agnostic solid tumors. Given the small sample size of the analysis (n=37), the results should be interpreted with caution.

General Information			
Goal of ER analysis		To explore relationships between selpercatinib exposure and overall response rate (ORR) with all available response data from the LOXO-RET-17001 study for patients with tissue-agnostic solid tumors	
Study Included		LOXO-RET-17001 (data cut-off date 15 June 2021)	
Endpoint		Primary: overall response rate (ORR)	
No. of Patients (total, and with individual PK)		37	
Population Characteristics (Table 19-6)	General	Age median 500 yr (21.0 - 85.0) Weight median 64.8kg (40.6 - 105) Male N=17 (45.9%) Female N=20 (54.1%) White N=25 (67.6%) Other N =12 (32.4%)	
	Pediatrics (if any)	No patients less than age 12	
Dose(s) Included		80, 120, 160mg (Table 19-7)	
Exposure Metrics Explored (range)		Table 19-6	
Covariates Evaluated		Table 19-8	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		Exposure response analysis was performed using logistic regression	Acceptable
Model Parameter Estimates		N/A as no predictor was statistically significant	Acceptable
Model Evaluation		The full model analysis included Cmin_10 (Table 19-9) plus the other predictors (age, race, body weight, sex, ECOG status at baseline, prior radiation therapy, and prior surgical therapy). The stepwise removal	Acceptable

	process resulted in a model in which no predictor being statistically significant (p>0.05). The lack of any relationships may be due to the small sample size for this subgroup analysis (n=37).	
Covariates and Clinical Relevance	N/A as no predictor was statistically significant	Acceptable
Simulation for Specific Population	N/A as no predictor was statistically significant	Acceptable
Visualization of E-R relationships	Figure 19-8	Acceptable
Overall Clinical Relevance for ER	Although no clear exposure-response relationship was established for patients with tissue-agnostic solid tumors, considering the small sample size, majority patients on 160 mg BID, similarity of PK across tumor types, and that the ORR for the this subpopulation included in this exposure-response analysis was 43.2% (16 responders of 37 subjects) (ELIL-PMX-SELPERCATINIB-3499), the sponsor considers the data supportive of selpercatinib's efficacy in this population based on the totality of data, and the overall benefit-risk profile and effect observed from LIBRETTO-001.	Due to the limited number of patients (n=37), the result of the ER analysis is inconclusive.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	No Change	N/A

Table 18-6. Summary of Predictors Stratified by Response Status - TA Tumors

	Nonresponder (N=21)	Responder (N=16)	Overall (N=37)
Sex			
Female	10 (47.6%)	10 (62.5%)	20 (54.1%)
Male	11 (52.4%)	6 (37.5%)	17 (45.9%)
Race			
Other	5 (23.8%)	7 (43.8%)	12 (32.4%)
White	16 (76.2%)	9 (56.3%)	25 (67.6%)
Prior radiotherapy			
No	13 (61.9%)	11 (68.8%)	24 (64.9%)
Yes	8 (38.1%)	5 (31.3%)	13 (35.1%)
Prior surgery			
No	9 (42.9%)	8 (50.0%)	17 (45.9%)
Yes	12 (57.1%)	8 (50.0%)	20 (54.1%)
ECOG status at baseline			
0	6 (28.6%)	7 (43.8%)	13 (35.1%)
1	14 (66.7%)	9 (56.3%)	23 (62.2%)
2	1 (4.8%)	0 (0%)	1 (2.7%)
Age (years)			
Mean (SD)	56.4 (17.9)	44.1 (9.52)	51.1 (15.9)
Median [min, max]	61.0 [21.0, 85.0]	44.0 [31.0, 62.0]	50.0 [21.0, 85.0]
Body weight (kg)			
Mean (SD)	72.6 (16.1)	61.1 (17.3)	67.6 (17.4)
Median [min, max]	76.0 [40.6, 105]	58.6 [40.8, 101]	64.8 [40.6, 105]
AUC24 (ng•hr/mL)			
Mean (SD)	29900 (14300)	38000 (17300)	33400 (16000)
Median [min, max]	30100 [12400, 55700]	39700 [4580, 82700]	32500 [4580, 82700]
Cmin (ng/mL)			
Mean (SD)	1010 (555)	747 (486)	898 (536)
Median [min, max]	1000 [293, 2030]	576 [112, 2270]	773 [112, 2270]
Cmax (ng/mL)			
Mean (SD)	1840 (792)	2300 (887)	2040 (854)
Median [min, max]	1780 [636, 3460]	2290 [438, 4190]	2030 [438, 4190]
AUC24_10 dose average (ng•h/mL)			
Mean (SD)	40900 (25200)	38300 (17500)	39800 (22000)

	Nonresponder (N=21)	Responder (N=16)	Overall (N=37)
Median [min, max]	38700 [11400, 111000]	40000 [9440, 82000]	39100 [9440, 111000]
Cmin_10 dose average (ng/mL)			
Mean (SD)	1140 (807)	775 (480)	984 (702)
Median [min, max]	980 [260, 3630]	707 [110, 2200]	817 [110, 3630]
Cmax_10 dose average (ng/mL)			
Mean (SD)	2420 (1230)	2390 (870)	2410 (1080)
Median [min, max]	2280 [685, 5220]	2390 [987, 4190]	2390 [685, 5220]

Source: overall response 03MAR2022 – TA.Rmd
Abbreviations: AUC=area under the plasma concentration-time curve; Cmax=maximum selpercatinib concentration; Cmin=minimum selpercatinib concentration; AUC_10= area under the plasma concentration-time curve averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event; Cmax_10=maximum selpercatinib concentration averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event; Cmin_10=minimum selpercatinib concentration averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event; ECOG=Eastern Cooperative Oncology Group; max=maximum, min=minimum, N=number of subjects; SD=standard deviation; TA=tissue agnostic

Table 18-7. Summary of dose information for TA Tumors

	Non-responder (N=21)	Responder (N=16)	Overall (N=37)
AMTF			
0	0 (0%)	0 (0%)	0 (0%)
20	0 (0%)	0 (0%)	0 (0%)
40	0 (0%)	0 (0%)	0 (0%)
60	0 (0%)	0 (0%)	0 (0%)
80	1 (4.8%)	2 (12.5%)	3 (8.1%)
120	5 (23.8%)	1 (6.3%)	6 (16.2%)
160	15 (71.4%)	13 (81.3%)	28 (75.7%)
200	0 (0%)	0 (0%)	0 (0%)
240	0 (0%)	0 (0%)	0 (0%)

Source: derived from overall response 03MAR2022 – TA.Rmd
Abbreviations AMTF = dose (mg) ; N=number of subjects; TA=tissue agnostic

Table 18-8. Predictors Evaluated in the Efficacy Exposure-Response Model

Predictor	Description	Reason for Investigation
LOXO-292 dose	Nominal dose in mg This dose represents the dose at the time or closest prior to the time of response or the dose at the highest exposure for nonresponders.	Overall response may be related to drug exposure.
LOXO-292 AUC24	Area under the plasma concentration-time curve over 24 hours at time of response for the responder and last treatment period for the nonresponder	Overall response may be related to drug exposure.
LOXO-292 Cmin	Minimum plasma concentration at time of response for the responder and last treatment period for the nonresponder	Overall response may be related to drug exposure.
LOXO-292 Cmax	Maximum plasma concentration at time of response for the responder and last treatment period for the nonresponder	Overall response may be related to drug exposure.
LOXO-292 AUC24_10	Area under the plasma concentration-time curve over 24 hours averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event	Overall response may be related to drug exposure.
LOXO-292 Cmin_10	Minimum selpercatinib concentration averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event	Overall response may be related to drug exposure.
LOXO-292 Cmax_10	Maximum selpercatinib concentration averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event	Overall response may be related to drug exposure.
Age	Age in years	Overall response may be related to age.
Body weight	Body weight in kg	Overall response may be related to body weight.
Sex	Male or female	Possible sex differences.
ECOG status at baseline	0, 1, or 2	Overall response may be related to ECOG at baseline.
Prior radiation therapy	Yes or No, binary variable	Overall response may be related to prior radiation therapy.

Predictor	Description	Reason for Investigation
Prior surgical therapy	Yes or No, binary variable	Overall response may be related to prior surgical therapy.

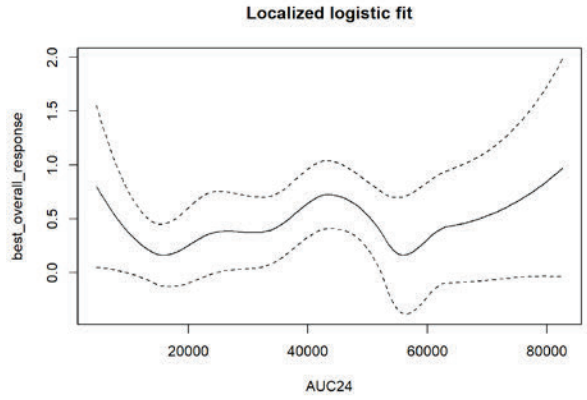
Abbreviations: AE=adverse event; AUC24=area under the plasma concentration-time curve over 24 hours at steady state; Cmax=maximum selpercatinib concentration; Cmin=minimum selpercatinib concentration; ECOG=Eastern Cooperative Oncology Group

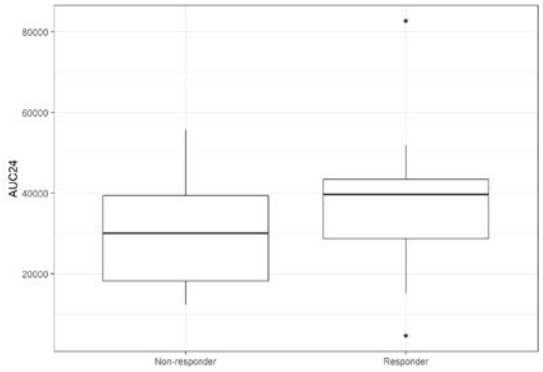
Table 18-9. AIC Values from Univariate Exposure-Response Analysis - TA Tumors

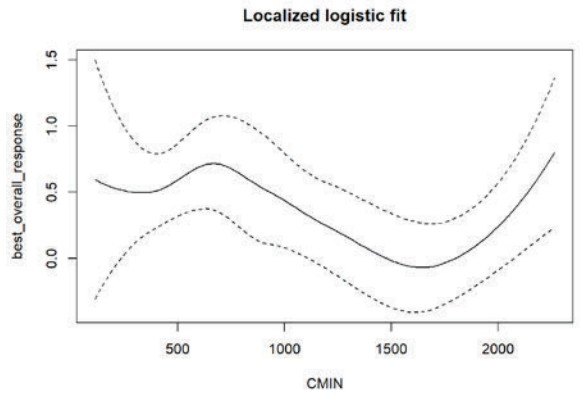
Model	AIC
Response - Cmin_10	51.66
Response - Cmax	51.8
Response - AUC24	52.11
Response - Cmin	52.18
Response - Dose (categorical)	53.9
Response - AUC24_10	54.48
Response - Dose (continuous)	54.6
Response - Cmax_10	54.61

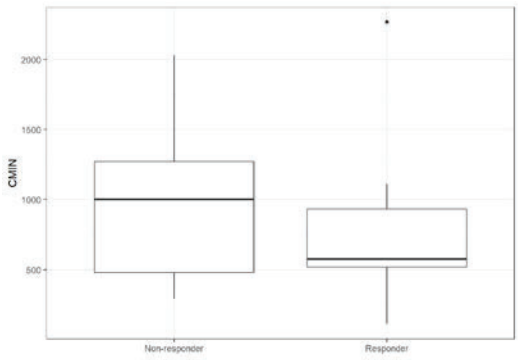
Source: overall response 03MAR2022 - TA.Rmd

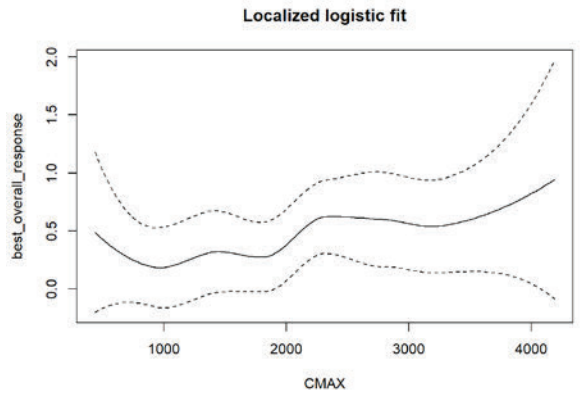
Abbreviations: AIC=Akaike information criterion; AUC24=area under the plasma concentration time curve over 24 hours at steady state; AUC24_10=area under the plasma concentration-time curve over 24 hours averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event; Cmax=maximum selpercatinib concentration; Cmax_10=maximum selpercatinib exposure averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event; Cmin=minimum selpercatinib concentration; Cmin_10= minimum selpercatinib exposure averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event; TA=tumor agnostic

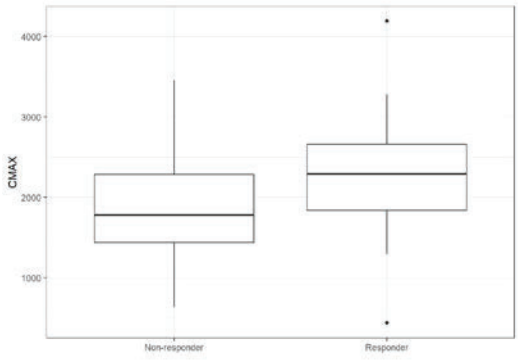


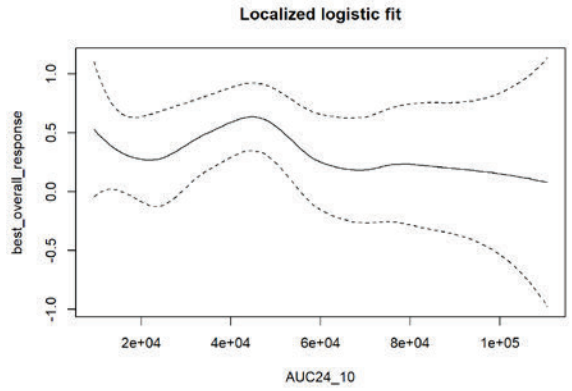


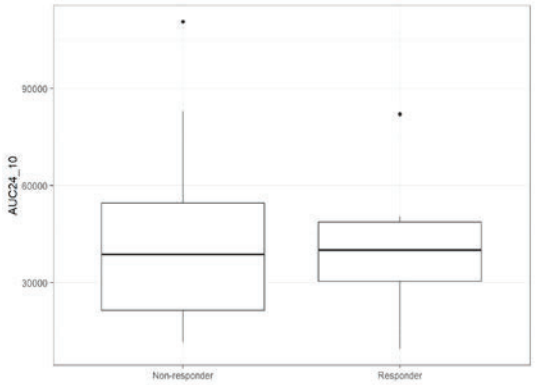


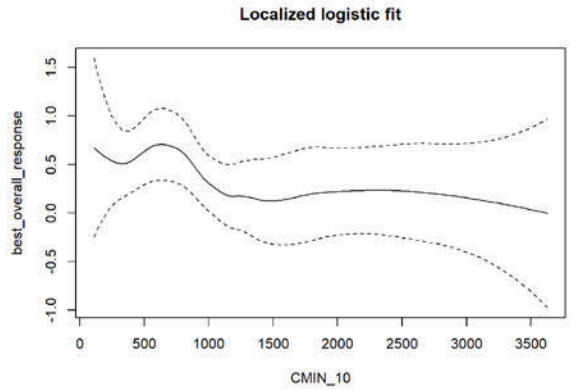


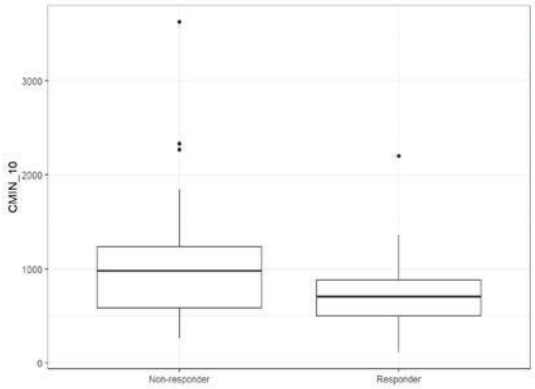


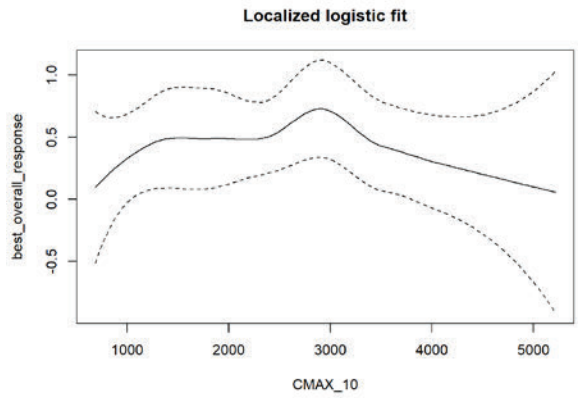


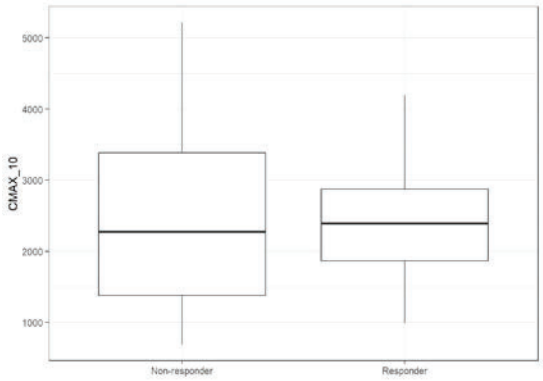




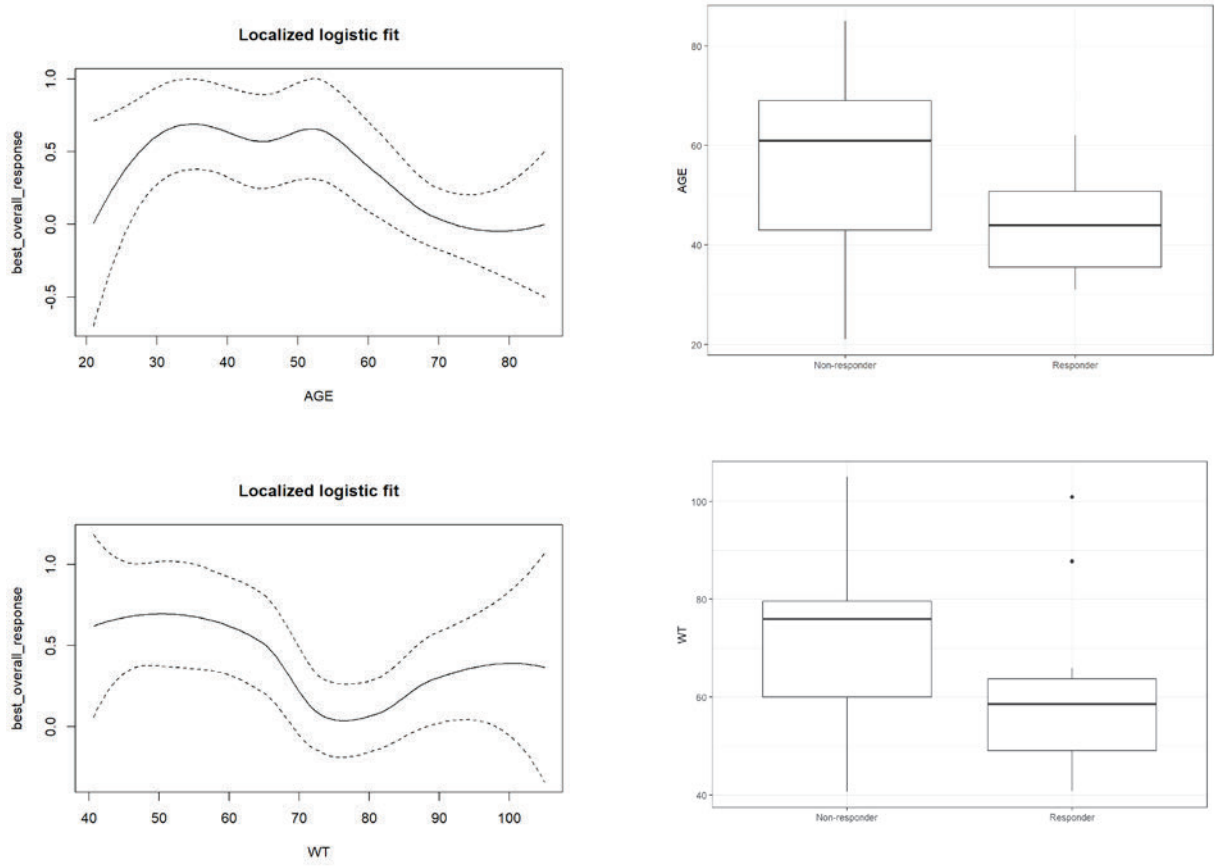








Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.



Source: overall response 03MAR2022 - TA.Rmd
Abbreviations: AUC24=area under the plasma concentration-time curve over 24 hours at steady state; AUC24_10=area under the plasma concentration-time curve over 24 hours averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event; CMAX=maximum selpercatinib concentration (at steady state); CMAX_10=maximum plasma concentration averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event; CMIN=minimum selpercatinib concentration (at steady state); CMIN_10=minimum plasma concentration averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event; TA=tissue agnostic; WT=body weight

Figure 19-8. Boxplots and Logistic Regressions for Increases in Response Versus Continuous Predictors – patient with tissue-agnostic solid tumors

19.4.2.3. ER (safety) Executive Summary

The FDA's Assessment:

The applicant evaluated the relationship between selpercatinib plasma exposures and the following adverse reactions: increases in ALT, increases in AST, hypertension, and hypersensitivity for all subjects and for the subsets of subjects

with MTC only or tissue-agnostic *RET* fustion-positive tumors only (data cut-off date 06/15/2021) from LIBRETTO-001. No increased risk was observed with increased selpercatinib exposure. This result was similar to previous submissions. The results of the ER safety analysis was considered acceptable.

19.4.2.4. ER (safety) Assessment Summary

The Applicant's Position:

For patients with tissue-agnostic solid tumors, the exposure-response analyses for safety did not identify any treatment-related predictors.

The safety exposure-response analysis was conducted using all available data from the LIBRETTO-001 study (15 June 2021 cut-off date) for the AEs of interest (increases in ALT, increases in AST, hypertension, and hypersensitivity) for all patients, and for patients with tissue-agnostic solid tumor only. Possible predictors included selpercatinib steady-state AUC_{0-24}, dose reduction status, age, body weight, and sex. It was found that
The safety exposure-response analysis results for the 4 AEs of interest with all data appeared to be similar to those previously reported for all patients. None of the AEs of interest listed above showed an increased risk with increases in selpercatinib exposure for all patients. In the overall population, subjects with a dose reduction had higher risk of all AEs. However, this may be due to the dose reductions when AEs occurred. Steady-state AUC_{0-24} was the predictor for ALT, AST, and hypertension AEs. For the AE of hypertension, compared to the reference age of 58 years, the risk of the AE is higher in subjects older than 58 years, whereas the risk was lower in subjects younger than 58 years.
For patients with tissue-agnostic solid tumors, no statistically significant predictor was identified for increases in ALT and increases in AST. Only age was identified as a predictor of AE for hypertension. No hypersensitivity AE were recorded in this subpopulation. Given the small sample size of the analysis (n=37), the results should be interpreted with caution.

General Information	
Goal of ER analysis	To explore relationships between selpercatinib exposure and of adverse events (AEs) of interest (i.e., increase in alanine aminotransferase [ALT], increase in aspartate aminotransferase [AST], hypertension, and hypersensitivity) with all available AE data from all patients from the LOXO-RET-17001 study (data cut-off date 15 June 2021), and subjects with tissue-agnostic solid tumors only
Study Included	LOXO-RET-17001

Population Included		all patients from the LOXO-RET-17001 study (data cut-off date 15 June 2021), and patients with tissue-agnostic solid tumors only	
Endpoint		increase in alanine aminotransferase [ALT], increase in aspartate aminotransferase [AST], hypertension, and hypersensitivity	
No. of Patients (total, and with individual PK)		767 patients in total Including 37 patients with tissue-agnostic solid tumors	
Population Characteristics (Table 19-10, Table 19-11, Table 19-12, Table 19-13)	General	Age median 58.0yr (15.0 - 92.0) Weight median 67.4kg (26.8 – 179) Male N=392 (51.1%) Female N= 375(48.9%) White N= 520 (67.8%) Asian N= 183 (23.9%) Black N=25 (3.3%) Other N=39 (5.1%)	
	Organ impairment	N/A	
	Pediatrics (if any)	No patients less than age 12	
	Geriatrics (if any)	Patients over 65 were included in the analysis.	
Dose(s) Included		Starting dose of 20, 40, 60, 80,120, 160, 200, 240mg *(*Table 19-10, Table 19-11, Table 19-12, Table 19-13*)*	
Exposure Metrics Explored (range)		Table 19-10 and Table 19-15 for analysis of ALT AE Table 19-11 and Table 19-16 for analysis of AST AE Table 19-12 and Table 19-17 for analysis of hypertension AE Table 19-13 and Table 19-18 for analysis of hypersensitivity AE	
Covariates Evaluated		Table 19-14	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		Logistic regression was used for exploratory analysis Exploratory analyses suggested that a logistic regression analysis could not accurately capture the impact of dose reductions and the longer duration of the study. Thus, a time-to-event analysis for the probability of the first AE of each endpoint was performed using Cox proportional hazard model	Acceptable
Model Parameter Estimates		***Analysis with all patients*** model parameter estimates were visualized in	Acceptable

	Figure 19-9 (AUC24 and dose reduction) for ALT AE Figure 19-11 (AUC24 and dose reduction) for AST AE Figure 19-13 (AUC24, dose reduction, and age) for hypertension AE Figure 19-15 (Dose reduction) for hypersensitivity AE Final time-to-event model hazard ratios were reported in Figure 19-10 (AUC24 and dose reduction) for ALT AE Figure 19-12 (AUC24 and dose reduction) for AST AE Figure 19-14 (AUC24, dose reduction, and age) for hypertension AE Figure 19-16 (Dose reduction) for hypersensitivity AE ***Analysis with patients with tissue-agnostic solid tumors*** For ALT and AST, the Cox proportional hazard model was not developed for patients with tissue-agnostic solid tumors, because the logistic regression analysis showed that no predictor was significant. For hypertension, the final model for patients with tissue-agnostic solid tumors included only age as a predictor of time to first hypertensive AE ($p<0.05$). Given that no selpercatinib exposure metrics were found to be a significant predictor of the AE event, a Cox proportional hazard model was not developed, and a logistic regression model was used instead. For hypersensitivity, there were no hypersensitivity AEs in patients with tissue-agnostic solid tumors; hence, no analysis was conducted.	
Model Evaluation	*VPC of ALT AE for All Subjects* Figure 19-24	Acceptable

	Figure 19-25 *VPC of AST AE for All Subjects* Figure 19-26 Figure 19-27 *VPC of Hypertension AE for All Subjects* Figure 19-28 Figure 19-29 Figure 19-30 *VPC of Hypersensitivity AE for All Subjects* Figure 19-31	
Covariates and Clinical Relevance	Summary of E-R Safety Analysis Predictors are listed in Table 19-19 **Analysis of all patients,** None of the AEs of interest showed an increased risk with increases in selpercatinib exposure for all patients. In the overall population, subjects with a dose reduction had higher risk of all AEs. However, this may be due to the dose reductions when AEs occurred. Steady-state AUC_{0-24} was the predictor for ALT, AST, and hypertension AEs. For the AE of hypertension, compared to the reference age of 58 years, the risk of the AE is higher in subjects older than 58 years, whereas the risk was lower in subjects younger than 58 years. **Analysis for patients with tissue-agnostic solid tumors** no statistically significant predictor was identified for increases in ALT and increases in AST. Only age was identified as a predictor of AE for hypertension. No hypersensitivity AE were recorded in this subpopulation. Given the small sample size of the	Acceptable

	analysis (n=37), the results should be interpreted with caution.	
Simulation for Specific Population	N/A as no simulation was performed	Acceptable
Visualization of E-R relationships	*Kaplan-Meier Plot of ALT AE for All Subjects* Figure 19-17 Figure 19-18 *Kaplan-Meier Plot of AST AE for All Subjects* Figure 19-19 Figure 19-20 *Kaplan-Meier Plot of Hypertension AE for All Subjects* Figure 19-21 Figure 19-22 *Kaplan-Meier Plot of Hypersensitivity AE for All Subjects* Figure 19-23	Acceptable
Overall Clinical Relevance for ER	None of the AEs of interest showed an increased risk with increases in selpercatinib exposure for all patients. For patients with tissue-agnostic solid tumors, the exposure-response analyses for safety did not identify any treatment-related predictors.	Acceptable
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	no change	N/A

Table 18-10. Summary of Predictors Stratified by ALT AE

	No AE (N=675)	AE (N=92)	Overall (N=767)
Sex			
Male	343 (50.8%)	49 (53.3%)	392 (51.1%)
Female	332 (49.2%)	43 (46.7%)	375 (48.9%)
Race			
White	463 (68.6%)	57 (62.0%)	520 (67.8%)
Asian	152 (22.5%)	31 (33.7%)	183 (23.9%)
Black	24 (3.6%)	1 (1.1%)	25 (3.3%)
Other	36 (5.3%)	3 (3.3%)	39 (5.1%)
Tumor group			
NSCLC	299 (44.3%)	53 (57.6%)	352 (45.9%)
MTC	288 (42.7%)	27 (29.3%)	315 (41.1%)
Other	58 (8.6%)	5 (5.4%)	63 (8.2%)
Tissue agnostic	30 (4.4%)	7 (7.6%)	37 (4.8%)
Had dose reduction			
No reduction	420 (62.2%)	21 (22.8%)	441 (57.5%)
Reduction	255 (37.8%)	71 (77.2%)	326 (42.5%)
Age (years)			
Mean (SD)	56.9 (14.3)	59.3 (12.0)	57.1 (14.1)
Median [min, max]	58.0 [15.0, 92.0]	60.0 [25.0, 86.0]	58.0 [15.0, 92.0]
Body weight (kg)			
Mean (SD)	71.2 (19.6)	71.1 (21.2)	71.2 (19.7)
Median [min, max]	67.3 [26.8, 177]	68.0 [33.9, 179]	67.4 [26.8, 179]
AUC24 (ng•h/mL)			
Mean (SD)	52900 (28800)	42000 (25200)	51600 (28600)
Median [min, max]	47500 [1000, 227000]	39700 [0, 110000]	46700 [0, 227000]
AUC24_10 dose average (ng•h/mL)			
Mean (SD)	48000 (27900)	49700 (25600)	48200 (27700)
Median [min, max]	41800 [1450, 230000]	47400 [4580, 148000]	42400 [1450, 230000]
Cmin (ng/mL)			
Mean (SD)	1390 (1010)	1120 (778)	1360 (989)
Median [min, max]	1130 [18.7, 7660]	1020 [0, 3430]	1120 [0, 7660]
Cmin_10 dose average (ng/mL)			
Mean (SD)	1300 (961)	1300 (823)	1300 (945)

	No AE (N=675)	AE (N=92)	Overall (N=767)
Median [min, max]	1070 [29.9, 7460]	1110 [98.6, 5010]	1090 [29.9, 7460]
Cmax (ng/mL)			
Mean (SD)	2920 (1370)	2430 (1250)	2860 (1360)
Median [min, max]	2670 [87.6, 10800]	2320 [0, 5880]	2590 [0, 10800]
Cmax_10 dose average (ng/mL)			
Mean (SD)	2870 (1350)	2960 (1260)	2880 (1340)
Median [min, max]	2620 [117, 10700]	2800 [251, 6950]	2650 [117, 10700]
Dose[a] (mg)			
0	0 (0%)	8 (8.7%)	8 (1.0%)
20	3 (0.4%)	1 (1.1%)	4 (0.5%)
40	1 (0.1%)	2 (2.2%)	3 (0.4%)
60	6 (0.9%)	0 (0%)	6 (0.8%)
80	8 (1.2%)	5 (5.4%)	13 (1.7%)
120	16 (2.4%)	6 (6.5%)	22 (2.9%)
160	631 (93.5%)	69 (75.0%)	700 (91.3%)
180	1 (0.1%)	0 (0%)	1 (0.1%)
200	2 (0.3%)	1 (1.1%)	3 (0.4%)
240	7 (1.0%)	0 (0%)	7 (0.9%)
Starting Dose (mg)			
20	15 (2.2%)	1 (1.1%)	16 (2.1%)
40	15 (2.2%)	1 (1.1%)	16 (2.1%)
60	11 (1.6%)	1 (1.1%)	12 (1.6%)
80	18 (2.7%)	2 (2.2%)	20 (2.6%)
120	16 (2.4%)	2 (2.2%)	18 (2.3%)
160	592 (87.7%)	84 (91.3%)	676 (88.1%)
200	2 (0.3%)	1 (1.1%)	3 (0.4%)
240	6 (0.9%)	0 (0%)	6 (0.8%)

Source: Safety-ER-Analysis-04MAR2022.Rmd

[a] A dose of 0 indicates that the subject did not take a dose prior to the time of the AE, or the AE occurred more than 100 hours after the last dose. Dose is defined as the dose at the time of the AE or of the highest exposure for subjects who did not experience an AE.

Note: Values are presented as n (%) for categorical variables and mean (standard deviation) and median [min, max] for continuous variables.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AUC=area under the plasma concentration-time curve; Cmax=maximum concentration; Cmin=minimum concentration; AUC_10=area under the plasma concentration-time curve averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event; Cmax_10=maximum selpercatinib concentration averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event; Cmin_10=minimum selpercatinib concentration averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event; max=maximum; min=minimum; MTC=medullary thyroid cancer; N=number of subjects; NSCLC=non-small cell lung cancer; SD=standard deviation

Table 18-11. Summary of Predictors Stratified by AST AE

	No AE (N=679)	AE (N=88)	Overall (N=767)
Sex			
Male	345 (50.8%)	47 (53.4%)	392 (51.1%)
Female	334 (49.2%)	41 (46.6%)	375 (48.9%)
Race			
White	463 (68.2%)	57 (64.8%)	520 (67.8%)
Asian	159 (23.4%)	24 (27.3%)	183 (23.9%)
Black	23 (3.4%)	2 (2.3%)	25 (3.3%)
Other	34 (5.0%)	5 (5.7%)	39 (5.1%)
Tumor group			
NSCLC	312 (46.0%)	40 (45.5%)	352 (45.9%)
MTC	280 (41.2%)	35 (39.8%)	315 (41.1%)
Other	56 (8.2%)	7 (8.0%)	63 (8.2%)
Tissue agnostic	31 (4.6%)	6 (6.8%)	37 (4.8%)
Had dose reduction			
No reduction	413 (60.8%)	28 (31.8%)	441 (57.5%)
Reduction	266 (39.2%)	60 (68.2%)	326 (42.5%)
Age (years)			
Mean (SD)	56.9 (14.2)	58.9 (12.7)	57.1 (14.1)
Median [min, max]	58.0 [15.0, 92.0]	59.5 [25.0, 86.0]	58.0 [15.0, 92.0]
Body weight (kg)			
Mean (SD)	71.4 (19.8)	69.4 (19.7)	71.2 (19.7)
Median [min, max]	67.4 [26.8, 179]	67.5 [33.9, 122]	67.4 [26.8, 179]
AUC24 (ng•h/mL)			
Mean (SD)	52900 (28500)	37300 (29200)	51100 (29000)
Median [min, max]	47500 [1000, 227000]	33300 [0, 144000]	46600 [0, 227000]

	No AE (N=679)	AE (N=88)	Overall (N=767)
AUC24_10 dose average (ng•h/mL)			
Mean (SD)	47800 (27500)	49300 (30500)	48000 (27800)
Median [min, max]	41800 [1450, 230000]	42500 [4580, 148000]	41800 [1450, 230000]
Cmin (ng/mL)			
Mean (SD)	1390 (1010)	1000 (856)	1350 (1010)
Median [min, max]	1130 [18.7, 7660]	784 [0, 4140]	1110 [0, 7660]
Cmin_10 dose average (ng/mL)			
Mean (SD)	1300 (950)	1310 (953)	1300 (950)
Median [min, max]	1070 [29.9, 7460]	1070 [113, 5010]	1070 [29.9, 7460]
Cmax (ng/mL)			
Mean (SD)	2910 (1350)	2230 (1500)	2830 (1390)
Median [min, max]	2680 [87.6, 10800]	2150 [0, 7250]	2610 [0, 10800]
Cmax_10 dose average (ng/mL)			
Mean (SD)	2850 (1320)	2970 (1530)	2870 (1340)
Median [min, max]	2620 [117, 10700]	2630 [251, 7210]	2620 [117, 10700]
Dose[a] (mg)			
0	0 (0%)	14 (15.9%)	14 (1.8%)
20	3 (0.4%)	1 (1.1%)	4 (0.5%)
40	1 (0.1%)	2 (2.3%)	3 (0.4%)
60	6 (0.9%)	0 (0%)	6 (0.8%)
80	8 (1.2%)	6 (6.8%)	14 (1.8%)
120	15 (2.2%)	6 (6.8%)	21 (2.7%)
160	636 (93.7%)	58 (65.9%)	694 (90.5%)
180	1 (0.1%)	0 (0%)	1 (0.1%)
200	2 (0.3%)	1 (1.1%)	3 (0.4%)
240	7 (1.0%)	0 (0%)	7 (0.9%)
Starting Dose (mg)			
20	13 (1.9%)	3 (3.4%)	16 (2.1%)
40	15 (2.2%)	1 (1.1%)	16 (2.1%)
60	11 (1.6%)	1 (1.1%)	12 (1.6%)
80	16 (2.4%)	4 (4.5%)	20 (2.6%)
120	14 (2.1%)	4 (4.5%)	18 (2.3%)
160	602 (88.7%)	74 (84.1%)	676 (88.1%)
200	2 (0.3%)	1 (1.1%)	3 (0.4%)

	No AE (N=679)	AE (N=88)	Overall (N=767)
240	6 (0.9%)	0 (0%)	6 (0.8%)

Source: Safety-ER-Analysis-04MAR2022.Rmd

[a] A dose of 0 indicates that the subject did not take a dose prior to the time of the AE, or the AE occurred more than 100 hours after the last dose. Dose is defined as the dose at the time of the AE or of the highest exposure for subjects who did not experience an AE.

Note: Values are presented as n (%) for categorical variables and as mean (standard deviation) and median [min, max] for continuous variables.

Abbreviations: AE=adverse event; AST=aspartate aminotransferase; AUC=area under the plasma concentration-time curve; Cmax=maximum concentration; Cmin=minimum concentration; AUC_10=area under the plasma concentration-time curve averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event; Cmax_10=maximum selpercatinib concentration averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event; Cmin_10=minimum selpercatinib concentration averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event; max=maximum; min=minimum; MTC=medullary thyroid cancer; NSCLC=non-small cell lung cancer; SD=standard deviation

Table 18-12. Summary of Predictors Stratified by Hypertension AE

	No AE (N=618)	AE (N=149)	Overall (N=767)
Sex			
Male	317 (51.3%)	75 (50.3%)	392 (51.1%)
Female	301 (48.7%)	74 (49.7%)	375 (48.9%)
Race			
White	424 (68.6%)	96 (64.4%)	520 (67.8%)
Asian	147 (23.8%)	36 (24.2%)	183 (23.9%)
Black	19 (3.1%)	6 (4.0%)	25 (3.3%)
Other	28 (4.5%)	11 (7.4%)	39 (5.1%)
Tumor group			
NSCLC	287 (46.4%)	65 (43.6%)	352 (45.9%)
MTC	249 (40.3%)	66 (44.3%)	315 (41.1%)
Other	52 (8.4%)	11 (7.4%)	63 (8.2%)
Tissue agnostic	30 (4.9%)	7 (4.7%)	37 (4.8%)
Had dose reduction			
No reduction	368 (59.5%)	73 (49.0%)	441 (57.5%)
Reduction	250 (40.5%)	76 (51.0%)	326 (42.5%)

	No AE (N=618)	AE (N=149)	Overall (N=767)
Age (years)			
Mean (SD)	56.6 (14.0)	59.4 (13.9)	57.1 (14.1)
Median [min, max]	58.0 [15.0, 92.0]	62.0 [23.0, 88.0]	58.0 [15.0, 92.0]
Body weight (kg)			
Mean (SD)	70.3 (19.3)	74.9 (21.2)	71.2 (19.7)
Median [min, max]	66.5 [26.8, 179]	72.0 [40.8, 165]	67.4 [26.8, 179]
AUC24 (ng•h/mL)			
Mean (SD)	51900 (26400)	46700 (27800)	50900 (26800)
Median [min, max]	47500 [1000, 227000]	41500 [0, 172000]	46600 [0, 227000]
AUC24_10 dose average (ng•h/mL)			
Mean (SD)	47400 (26200)	49700 (26200)	47900 (26200)
Median [min, max]	41400 [1450, 230000]	44500 [11000, 172000]	42000 [1450, 230000]
Cmin (ng/mL)			
Mean (SD)	1360 (935)	1310 (968)	1350 (941)
Median [min, max]	1120 [18.7, 7660]	1080 [0, 6220]	1110 [0, 7660]
Cmin_10 dose average (ng/mL)			
Mean (SD)	1270 (896)	1390 (948)	1300 (907)
Median [min, max]	1050 [29.9, 7350]	1120 [98.6, 6170]	1060 [29.9, 7350]
Cmax (ng/mL)			
Mean (SD)	2880 (1260)	2690 (1370)	2840 (1290)
Median [min, max]	2690 [87.6, 10800]	2470 [0, 8840]	2620 [0, 10800]
Cmax_10 dose average (ng/mL)			
Mean (SD)	2850 (1280)	2940 (1340)	2870 (1290)
Median [min, max]	2630 [117, 10700]	2680 [713, 8670]	2640 [117, 10700]

	No AE (N=618)	AE (N=149)	Overall (N=767)
Dose[a] (mg)			
0	0 (0%)	1 (0.7%)	1 (0.1%)
20	3 (0.5%)	0 (0%)	3 (0.4%)
40	1 (0.2%)	2 (1.3%)	3 (0.4%)
60	6 (1.0%)	2 (1.3%)	8 (1.0%)
80	8 (1.3%)	7 (4.7%)	15 (2.0%)
120	16 (2.6%)	11 (7.4%)	27 (3.5%)
160	574 (92.9%)	125 (83.9%)	699 (91.1%)
180	1 (0.2%)	0 (0%)	1 (0.1%)
200	3 (0.5%)	0 (0%)	3 (0.4%)
240	6 (1.0%)	1 (0.7%)	7 (0.9%)
Starting Dose (mg)			
20	14 (2.3%)	2 (1.3%)	16 (2.1%)
40	14 (2.3%)	2 (1.3%)	16 (2.1%)
60	11 (1.8%)	1 (0.7%)	12 (1.6%)
80	14 (2.3%)	6 (4.0%)	20 (2.6%)
120	18 (2.9%)	0 (0%)	18 (2.3%)
160	539 (87.2%)	137 (91.9%)	676 (88.1%)
200	3 (0.5%)	0 (0%)	3 (0.4%)
240	5 (0.8%)	1 (0.7%)	6 (0.8%)

Source: Safety-ER-Analysis-04MAR2022.Rmd

[a] A dose of 0 indicates that the subject did not take a dose prior to the time of the AE, or the AE occurred more than 100 hours after the last dose. Dose is defined as the dose at time of the AE or of the highest exposure for subjects who did not experience an AE.

Note: Values are presented as n (%) for categorical variables and as mean (standard deviation) and median [min, max] for continuous variables.

Abbreviations: AE=adverse event; AUC=area under the plasma concentration-time curve; Cmax=maximum concentration; Cmin=minimum concentration; AUC_10=area under the plasma concentration-time curve averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event; Cmax_10=maximum selpercatinib concentration averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event; Cmin_10=minimum selpercatinib concentration averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event; max=maximum; min=minimum; MTC=medullary thyroid cancer; N=number of subjects; NSCLC=non-small cell lung cancer; SD=standard deviation

Table 18-13. Summary of Predictors Stratified by Hypersensitivity AE

	No AE (N=755)	AE (N=12)	Overall (N=767)
Sex			
Male	388 (51.4%)	4 (33.3%)	392 (51.1%)
Female	367 (48.6%)	8 (66.7%)	375 (48.9%)
Race			
White	517 (68.5%)	3 (25.0%)	520 (67.8%)
Asian	174 (23.0%)	9 (75.0%)	183 (23.9%)
Black	25 (3.3%)	0 (0%)	25 (3.3%)
Other	39 (5.2%)	0 (0%)	39 (5.1%)
Tumor group			
NSCLC	342 (45.3%)	10 (83.3%)	352 (45.9%)
MTC	313 (41.5%)	2 (16.7%)	315 (41.1%)
Other	63 (8.3%)	0 (0%)	63 (8.2%)
Tissue agnostic	37 (4.9%)	0 (0%)	37 (4.8%)
Had dose reduction			
No reduction	440 (58.3%)	1 (8.3%)	441 (57.5%)
Reduction	315 (41.7%)	11 (91.7%)	326 (42.5%)
Age (years)			
Mean (SD)	57.1 (14.1)	57.4 (11.8)	57.1 (14.1)
Median [min, max]	58.0 [15.0, 92.0]	58.5 [30.0, 72.0]	58.0 [15.0, 92.0]
Body weight (kg)			
Mean (SD)	71.3 (19.8)	67.1 (10.5)	71.2 (19.7)
Median [min, max]	67.5 [26.8, 179]	65.9 [50.8, 83.6]	67.4 [26.8, 179]
AUC24 (ng•h/mL)			
Mean (SD)	53000 (28200)	53700 (27800)	53000 (28200)
Median [min, max]	47600 [1000, 227000]	45900 [0, 87500]	47600 [0, 227000]
AUC24_10 dose average (ng•h/mL)			
Mean (SD)	48000 (27700)	63800 (25400)	48200 (27700)
Median [min, max]	41600 [1450, 230000]	61700 [33100, 95900]	41700 [1450, 230000]
Cmin (ng/mL)			
Mean (SD)	1390 (998)	1440 (928)	1400 (996)
Median [min, max]	1130 [18.7, 7660]	1200 [0, 2790]	1130 [0, 7660]
Cmin_10 dose average (ng/mL)			
Mean (SD)	1300 (951)	1650 (795)	1310 (949)

	No AE (N=755)	AE (N=12)	Overall (N=767)
Median [min, max]	1070 [29.9, 7460]	1520 [627, 2810]	1090 [29.9, 7460]
Cmax (ng/mL)			
Mean (SD)	2920 (1340)	3090 (1450)	2920 (1340)
Median [min, max]	2690 [87.6, 10800]	2830 [0, 4730]	2690 [0, 10800]
Cmax_10 dose average (ng/mL)			
Mean (SD)	2870 (1330)	3720 (1410)	2880 (1340)
Median [min, max]	2630 [117, 10700]	3590 [2150, 6140]	2640 [117, 10700]
Dose[a] (mg)			
0	0 (0%)	1 (8.3%)	1 (0.1%)
20	3 (0.4%)	0 (0%)	3 (0.4%)
40	1 (0.1%)	0 (0%)	1 (0.1%)
60	6 (0.8%)	0 (0%)	6 (0.8%)
80	9 (1.2%)	0 (0%)	9 (1.2%)
120	18 (2.4%)	0 (0%)	18 (2.3%)
160	707 (93.6%)	11 (91.7%)	718 (93.6%)
180	1 (0.1%)	0 (0%)	1 (0.1%)
200	3 (0.4%)	0 (0%)	3 (0.4%)
240	7 (0.9%)	0 (0%)	7 (0.9%)
Starting Dose (mg)			
20	16 (2.1%)	0 (0%)	16 (2.1%)
40	16 (2.1%)	0 (0%)	16 (2.1%)
60	12 (1.6%)	0 (0%)	12 (1.6%)
80	20 (2.6%)	0 (0%)	20 (2.6%)
120	18 (2.4%)	0 (0%)	18 (2.3%)
160	664 (87.9%)	12 (100%)	676 (88.1%)
200	3 (0.4%)	0 (0%)	3 (0.4%)
240	6 (0.8%)	0 (0%)	6 (0.8%)

Source: Safety-ER-Analysis-04MAR2022.Rmd

[a] A dose of 0 indicates that the subject did not take a dose prior to the time of the AE, or the AE occurred more than 100 hours after the last dose. Dose is defined as the dose at time of the AE or of the highest exposure for subjects who did not experience an AE

Note: Values are presented as n (%) for categorical variables and as mean (standard deviation) and median [minimum, maximum] for continuous variables.

Abbreviations: AE=adverse event; AUC=area under the plasma concentration-time curve; Cmax=maximum concentration; Cmin=minimum concentration; AUC_10= area under the plasma concentration-time curve averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event; Cmax_10=maximum selpercatinib concentration averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did

not have an event; Cmin_10=minimum selpercatinib concentration averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study participation for subjects who did not have an event; max=maximum; min=minimum; MTC=medullary thyroid cancer; N=number of subjects; NSCLC=non-small cell lung cancer; SD=standard deviation

Table 18-14. Predictors Evaluated in the Safety Exposure-Response Model

Predictor	Description	Reason for Investigation
LOXO-292 AUC24	Area under the plasma concentration time curve over 24 hours at steady state when the AE occurred	AEs may be related to drug exposure.
Age	Age in years	AEs may be related to age.
Body weight	Body weight in kg	AEs may be related to body weight.
Sex	Male or female	Possible sex differences.
Dose reduction status	Subject had dose reduced during the study (Yes) or did not have a dose reduction (No)	AEs may be related to dose reductions.

Abbreviations: AE=adverse event; AUC24=area under the plasma concentration-time curve over 24 hours at steady state.

Table 18-15. Selpercatinib AUC24 Quartiles for ALT AE

Quartile	Range for All Subjects (ng•h/mL)
1 (lowest AUC24)	0, 32768
2	32855, 46669
3	46729, 65437
4 (highest AUC24)	65442, 227150

Source: Safety-ER-Analysis-04MAR2022.Rmd
Note: Quartile 1 includes the smallest selpercatinib AUCs, and Quartile 4 includes the largest selpercatinib AUCs.
Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AUC= area under the plasma concentration-time curve; AUC24=AUC over 24 hours at steady state.

Table 18-16. Selpercatinib AUC24 Quartiles for AST AE

Quartile	Range for All Subjects (ng•h/mL)
1 (lowest AUC24)	0, 31655
2	31704, 46618
3	46669, 65046
4 (highest AUC24)	65072, 227150

Source: Safety-ER-Analysis-04MAR2022.Rmd
Note: Quartile 1 includes the smallest selpercatinib AUCs, and Quartile 4 includes the largest selpercatinib AUCs.
Abbreviations: AE=adverse event; AST=aspartate aminotransferase; AUC=area under the plasma concentration-time curve; AUC24=AUC over 24 hours at steady state.

Table 18-17. Selpercatinib AUC24 Quartiles for Hypertension AE

Quartile	Range for All Subjects (ng•h/mL)
1 (lowest AUC24)	0, 32803
2	32855, 46618
3	46669, 64678
4 (highest AUC24)	64743, 227150

Source: Safety-ER-Analysis-04MAR2022.Rmd
Note: Quartile 1 includes the smallest selpercatinib AUCs, and Quartile 4 includes the largest selpercatinib AUCs.
Abbreviations: AE=adverse event; AUC= area under the plasma concentration-time curve; AUC24=AUC over 24 hours at steady state.

Table 18-18. Selpercatinib AUC24 Quartiles for Hypersensitivity AE

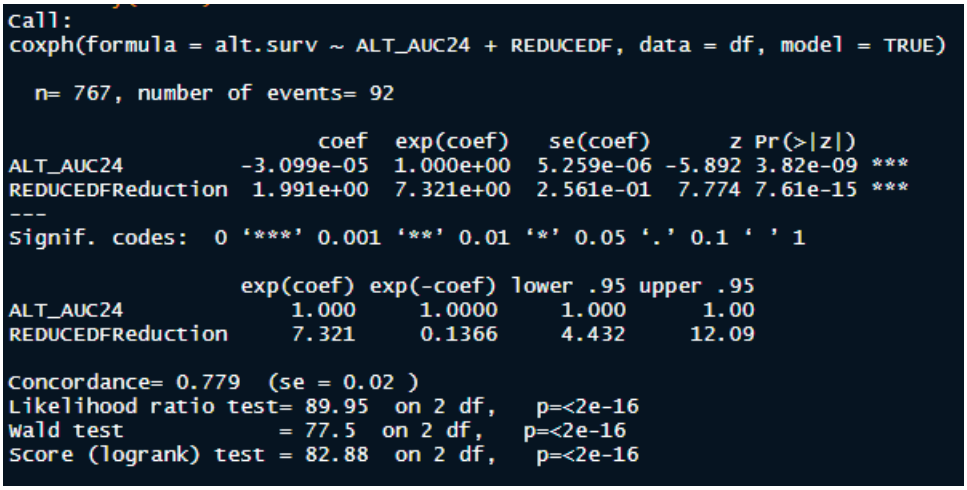
Quartile	Range for All Subjects (ng•h/mL)
1 (lowest AUC24)	0, 34309
2	34364, 47595
3	47617, 66630
4 (highest AUC24)	67204, 227150

Source: Safety-ER-Analysis-04MAR2022.Rmd
Note: Quartile 1 includes the smallest selpercatinib AUCs, and Quartile 4 includes the largest selpercatinib AUCs.
Abbreviations: AE=adverse event; AUC= area under the plasma concentration-time curve; AUC24=AUC over 24 hours at steady state

Table 18-19. Summary of E-R Safety Analysis Predictors

	Overall	Tissue-Agnostic Solid Tumors Only
Increase in ALT	AUC24 (Figure 19-17) Dose reduction (Figure 19-18)	No predictor
Increase in AST	AUC24 (Figure 19-19) Dose reduction (Figure 19-20)	No predictor
Hypertension	AUC24 (Figure 19-21) Dose reduction (Figure 19-22) Age	Age
Hypersensitivity	Dose reduction (Figure 19-23)	No AE data

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; AUC24=area under the plasma concentration-time curve over 24 hours at steady state; E-R=exposure-response



```
Call:
coxph(formula = alt.surv ~ ALT_AUC24 + REDUCEDF, data = df, model = TRUE)

  n= 767, number of events= 92

                        coef  exp(coef)   se(coef)      z Pr(>|z|)
ALT_AUC24         -3.099e-05  1.000e+00  5.259e-06 -5.892 3.82e-09 ***
REDUCEDFReduction  1.991e+00  7.321e+00  2.561e-01  7.774 7.61e-15 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

                  exp(coef) exp(-coef) lower .95 upper .95
ALT_AUC24             1.000     1.0000     1.000      1.00
REDUCEDFReduction     7.321     0.1366     4.432     12.09

Concordance= 0.779  (se = 0.02 )
Likelihood ratio test= 89.95  on 2 df,   p=<2e-16
Wald test            = 77.5  on 2 df,   p=<2e-16
Score (logrank) test = 82.88  on 2 df,   p=<2e-16
```

Source: Safety-ER-Analysis-04MAR2022.Rmd
Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AUC24=area under the plasma concentration-time curve over 24 hours at steady state

Figure 19-9. Final Time-to-Event Model Parameters for ALT AE With All Subjects

Characteristic	HR	CI
AUC24 (0 ng*hr/mL)	**1**	
5th Percentile AUC24 (15912 ng*hr/mL)	0.61	0.52, 0.72
Median AUC24 (46669 ng*hr/mL)	0.24	0.15, 0.38
95th Percentile AUC24 (99064 ng*hr/mL)	0.05	0.02, 0.13
Dose Reduction		
No (Reference)	1	--
Yes	7.32	4.43, 12.09

Source: Safety-ER-Analysis-04MAR2022.Rmd
Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AUC24=area under the plasma concentration-time curve over 24 hours at steady state; CI=confidence interval; HR=hazard ratio

Figure 19-10. Final Time to-Event Model Hazard Ratios for ALT AE With All Subjects

```
Call:
coxph(formula = ast.surv ~ AST_AUC24 + REDUCEDF, data = df, model = TRUE)

  n= 767, number of events= 88

                      coef  exp(coef)   se(coef)      z Pr(>|z|)
AST_AUC24         -3.479e-05  1.000e+00  5.231e-06 -6.650 2.93e-11 ***
REDUCEDFReduction  1.466e+00  4.333e+00  2.329e-01  6.296 3.06e-10 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

                  exp(coef) exp(-coef) lower .95 upper .95
AST_AUC24             1.000     1.0000     1.000      1.00
REDUCEDFReduction     4.333     0.2308     2.745      6.84

Concordance= 0.748  (se = 0.027 )
Likelihood ratio test= 74.32  on 2 df,   p=<2e-16
Wald test            = 70.9  on 2 df,   p=4e-16
Score (logrank) test = 66.28  on 2 df,   p=4e-15
```

Source: Safety-ER-Analysis-04MAR2022.Rmd
Abbreviations: AE=adverse event; AST=aspartate aminotransferase; AUC24=area under the plasma concentration-time curve over 24 hours at steady state

Figure 19-11. Final Time-to-Event Model Parameters for AST AE With All Subjects

Characteristic	HR	CI
AUC (0 ng*hr/mL)	**1**	
5th Percentile AUC24 (14244 ng*hr/mL)	0.61	0.53, 0.71
Median AUC24 (46618 ng*hr/mL)	0.2	0.12, 0.32
95th Percentile AUC24 (99172 ng*hr/mL)	0.03	0.01, 0.09
Dose Reduction		
No (Reference)	1	
Yes	4.33	2.75, 6.84

Source: Safety-ER-Analysis-04MAR2022.Rmd
Abbreviations: AE=adverse event; AST=aspartate aminotransferase; AUC=area under the plasma concentration-time curve; AUC24=area under the plasma concentration-time curve over 24 hours at steady state; CI=confidence interval; HR=hazard ratio

Figure 19-12. Final Time-to-Event Model Hazard Ratios for AST AE With All Subjects

```
Call:
coxph(formula = hyper.surv ~ HYPER_AUC24 + REDUCEDF + I(AGE -
    age50), data = df, model = TRUE)

  n= 767, number of events= 149

                       coef  exp(coef)   se(coef)      z Pr(>|z|)
HYPER_AUC24       -1.145e-05  1.000e+00  3.787e-06 -3.024  0.00250 **
REDUCEDFReduction  3.693e-01  1.447e+00  1.734e-01  2.130  0.03316 *
I(AGE - age50)     1.638e-02  1.017e+00  6.351e-03  2.579  0.00991 **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

                  exp(coef) exp(-coef) lower .95 upper .95
HYPER_AUC24           1.000     1.0000     1.000     1.000
REDUCEDFReduction     1.447     0.6912     1.030     2.032
I(AGE - age50)        1.017     0.9838     1.004     1.029

Concordance= 0.586  (se = 0.024 )
Likelihood ratio test= 18.84  on 3 df,   p=3e-04
Wald test            = 17.82  on 3 df,   p=5e-04
Score (logrank) test = 17.79  on 3 df,   p=5e-04
```

Source: Safety-ER-Analysis-04MAR2022.Rmd
Abbreviations: AE=adverse event; AUC24=area under the plasma concentration-time curve over 24 hours at steady state

Figure 19-13. Final Time-to-Event Model Parameters for Hypertension AE With All Subjects

Characteristic	HR	CI
AUC (0 ng*hr/mL)	**1**	--
5th Percentile AUC24 (16350 ng*hr/mL)	0.83	0.73, 0.94
Median AUC24 (46618 ng*hr/mL)	0.59	0.41, 0.83
95th Percentile AUC24 (98402 ng*hr/mL)	0.32	0.16, 0.67
Age (median 58 yr)	**1**	--
5th Percentile Age (33 yr)	0.66	0.49, 0.91
95th Percentile Age (78 yr)	1.39	1.08, 1.78
Dose Reduction		
No (Reference)	1	
Yes	1.45	1.03, 2.03

Source: Safety-ER-Analysis-04MAR2022.Rmd
Abbreviations: AE=adverse event; AUC=area under the plasma concentration-time curve; AUC24=area under the plasma concentration-time curve over 24 hours at steady state; CI=confidence interval; HR=hazard ratio

Figure 19-14. Final Time-to-Event Model Hazard Ratios for Hypertension AE With All Subjects

```
Call:
coxph(formula = sens.surv ~ REDUCEDF, data = df, model = TRUE)

  n= 767, number of events= 12

                    coef exp(coef) se(coef)     z Pr(>|z|)
REDUCEDFReduction  2.701    14.896    1.044 2.586  0.00971 **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

                  exp(coef) exp(-coef) lower .95 upper .95
REDUCEDFReduction      14.9    0.06713     1.923     115.4

Concordance= 0.747  (se = 0.04 )
Likelihood ratio test= 13.06  on 1 df,   p=3e-04
Wald test            = 6.69  on 1 df,   p=0.01
Score (logrank) test = 11.88  on 1 df,   p=6e-04
```

Source: Safety-ER-Analysis-04MAR2022.Rmd
Abbreviations: AE=adverse event

Figure 19-15. Final Time-to-Event Model Parameters for Hypersensitivity AE With All Subjects

Characteristic	HR	CI
Dose Reduction		
No (Reference)	1	--
Yes	14.9	1.92, 115.38

Source: Safety-ER-Analysis-04MAR2022.Rmd
Abbreviations: AE=adverse event; CI=confidence interval; HR=hazard ratio

Figure 19-16. Final Time-to-Event Model Hazard Ratios for Hypersensitivity AE With All Subjects

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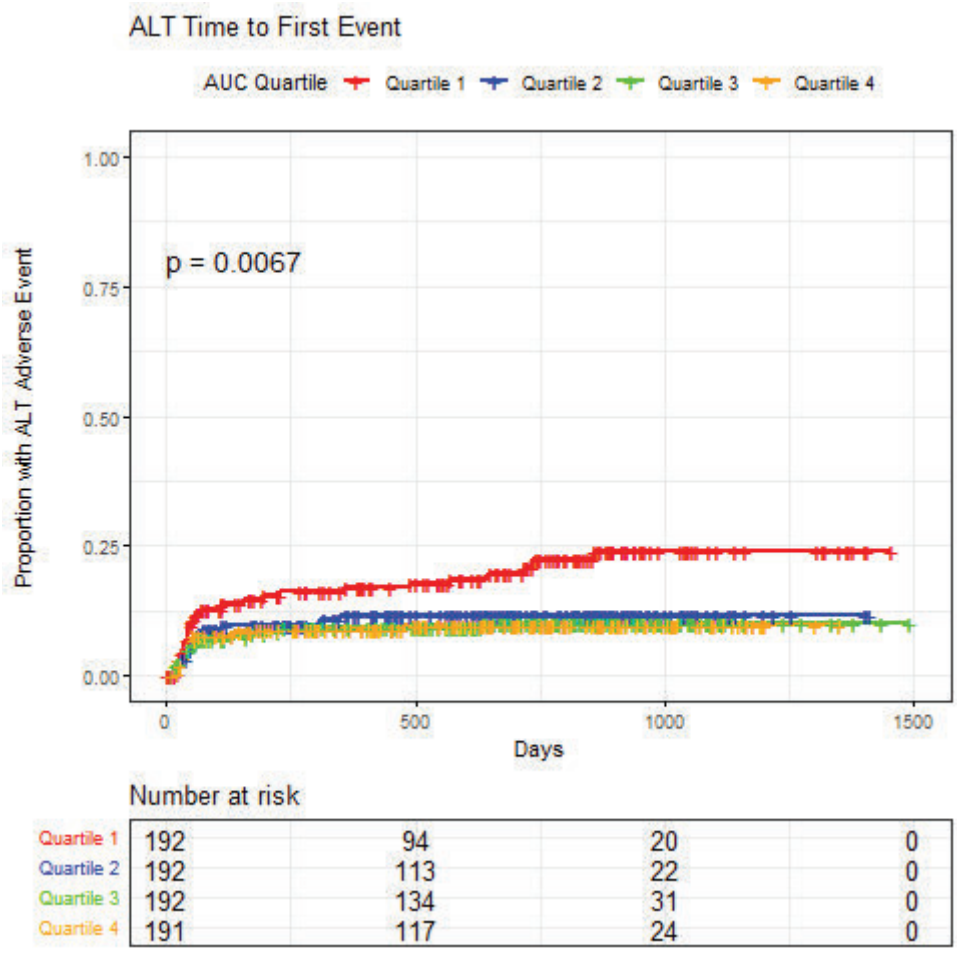
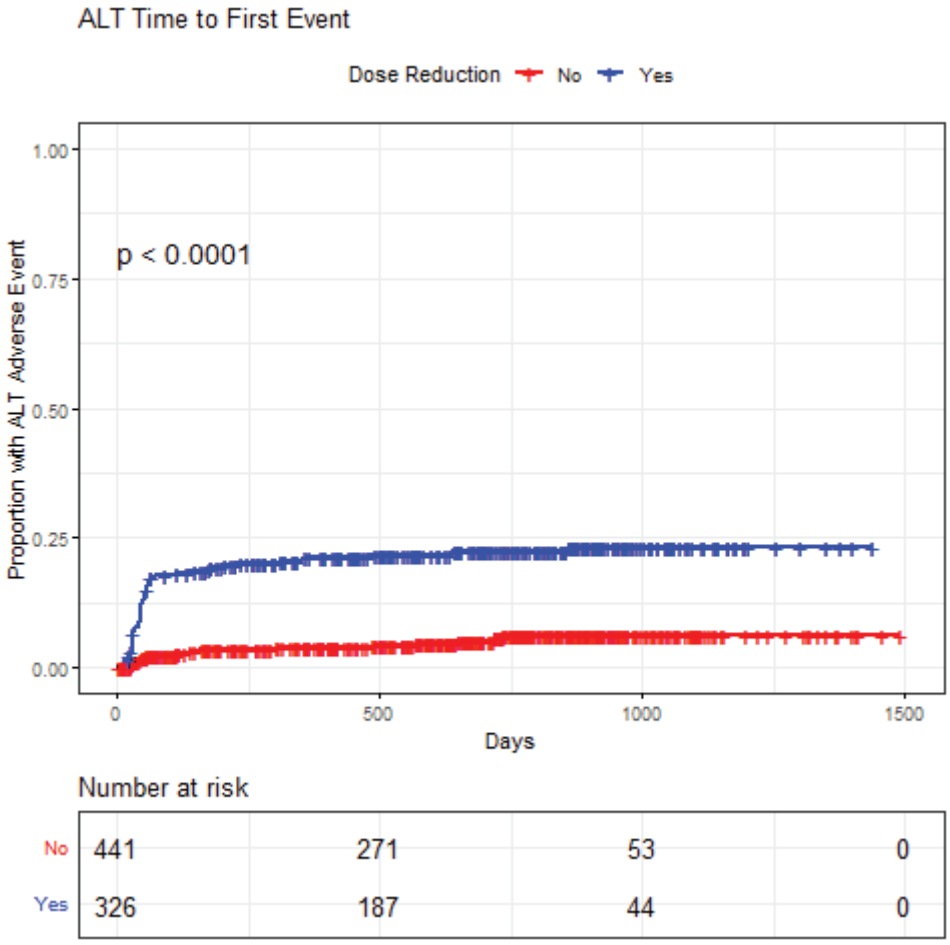


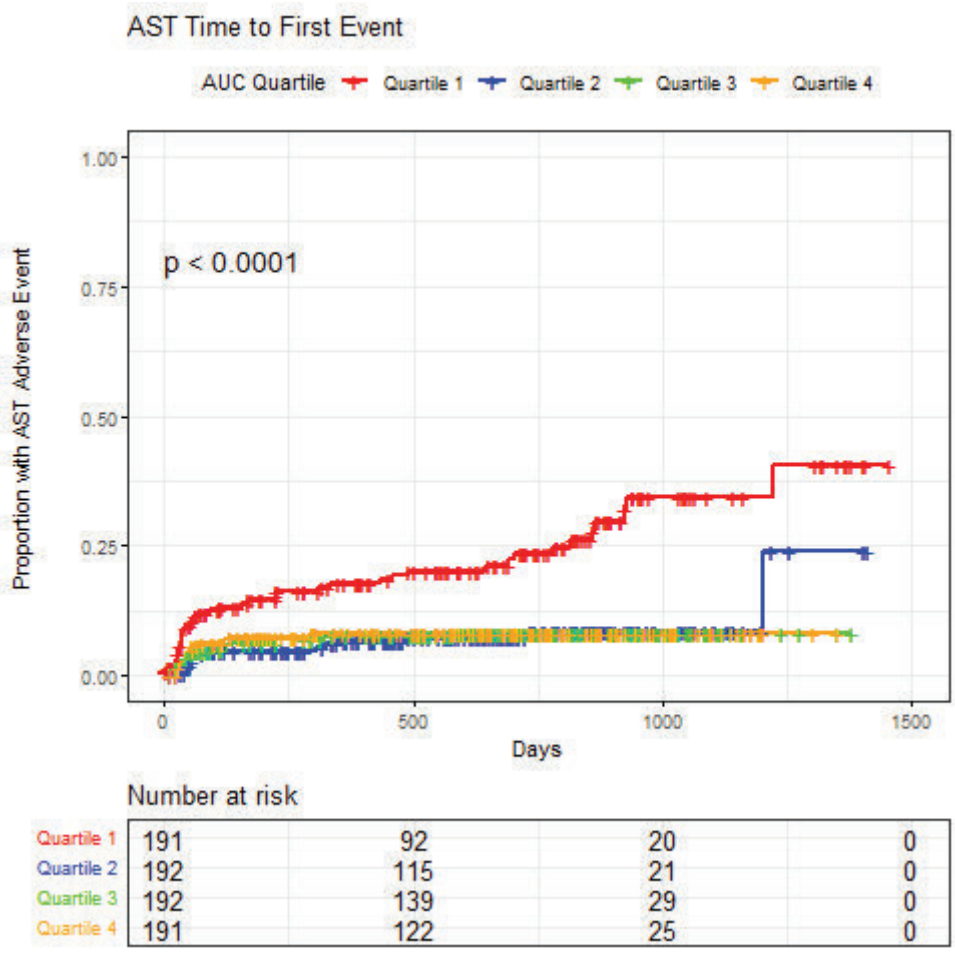
Source: Safety-ER-Analysis-04MAR2022.Rmd
Note: Quartile 1 includes the smallest selpercatinib AUCs, and Quartile 4 includes the largest selpercatinib AUCs (Table 19-15). Symbols represent time of censoring for subjects in that group.
Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AUC=area under the plasma concentration-time curve

Figure 19-17. Kaplan-Meier Plot of ALT AE for All Subjects Stratified by Selpercatinib AUC Quartiles



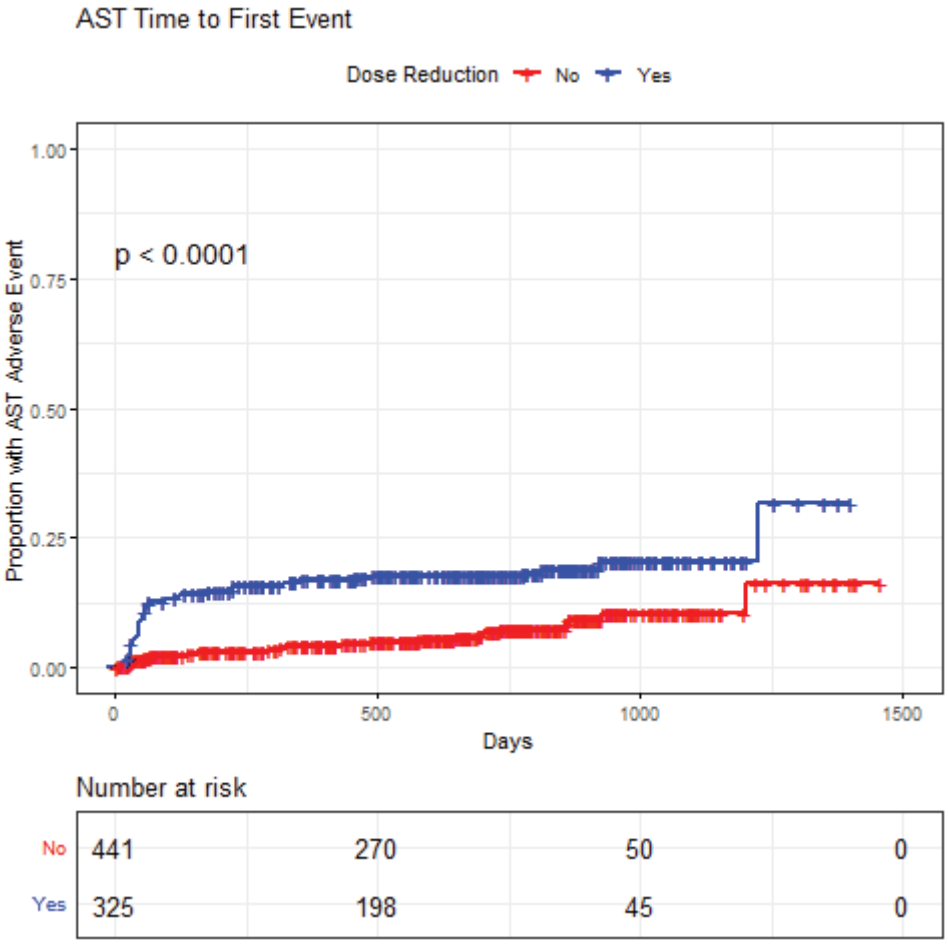
Source: Safety-ER-Analysis-04MAR2022.Rmd
Note: Symbols represent time of censoring for subjects in that group.
Abbreviations: AE=adverse event; ALT=alanine aminotransferase

Figure 19-18. Kaplan-Meier Plot of ALT AE for All Subjects Stratified by Selpercatinib Dose Reduction Status



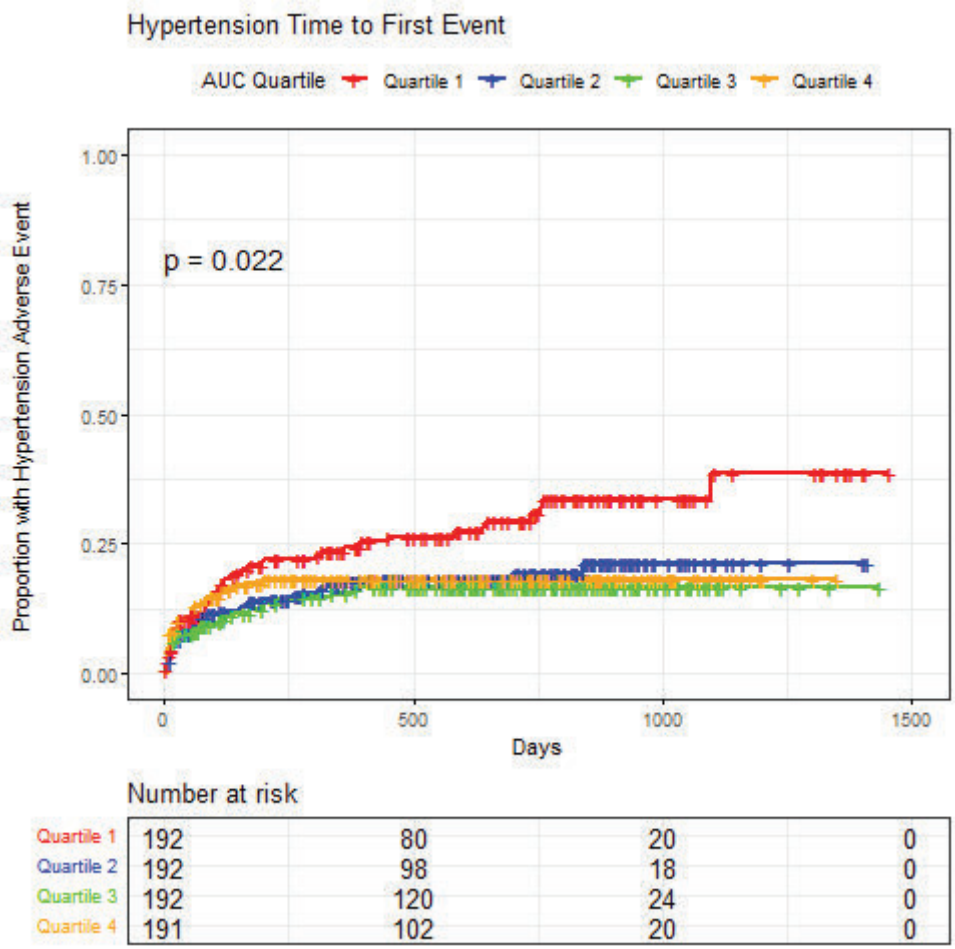
Source: Safety-ER-Analysis-04MAR2022.Rmd
Note: Quartile 1 includes the smallest selpercatinib AUCs, and Quartile 4 includes the largest selpercatinib AUCs (Table 19-16). Symbols represent time of censoring for subjects in that group.
Abbreviations: AE=adverse event; AST=aspartate aminotransferase; AUC=area under the plasma concentration-time curve

Figure 19-19. Kaplan-Meier Plot of AST AE for All Subjects Stratified by Selpercatinib AUC Quartiles



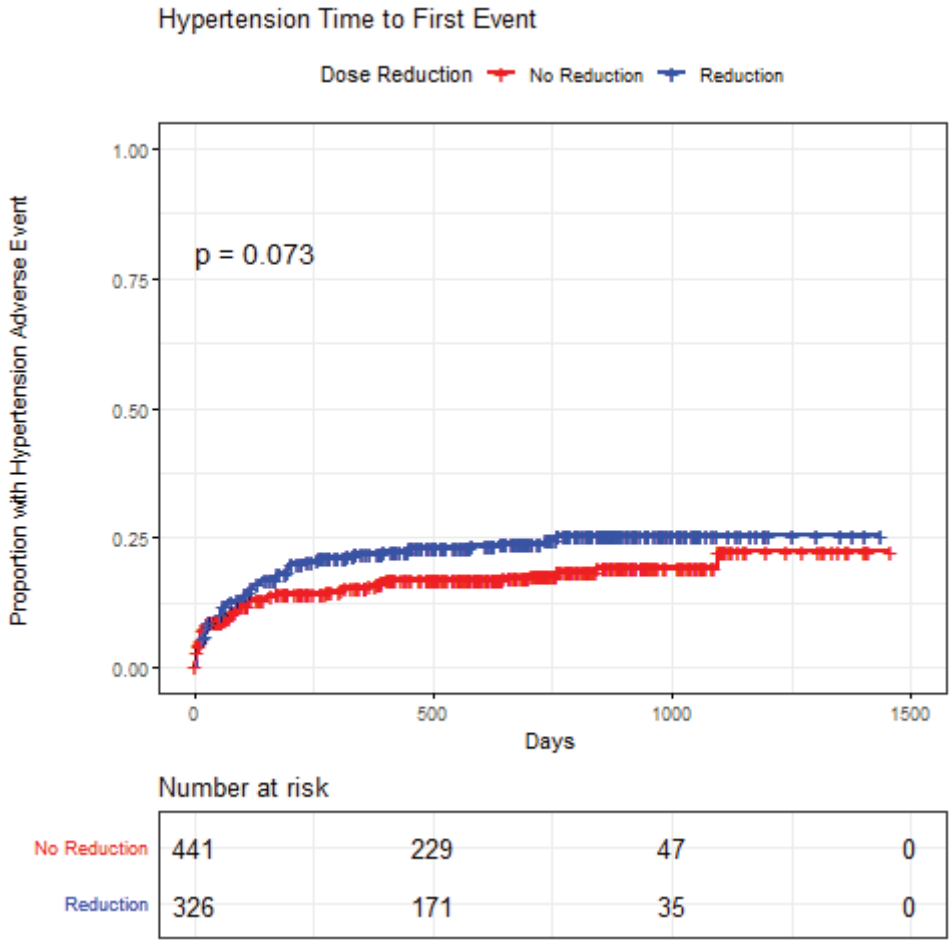
Source: Safety-ER-Analysis-04MAR2022.Rmd
Note: Symbols represent time of censoring for subjects in that group.
Abbreviations: AE=adverse event; AST=aspartate aminotransferase

Figure 19-20. Kaplan-Meier Plot of AST AE for All Subjects Stratified by Selpercatinib Dose Reduction Status



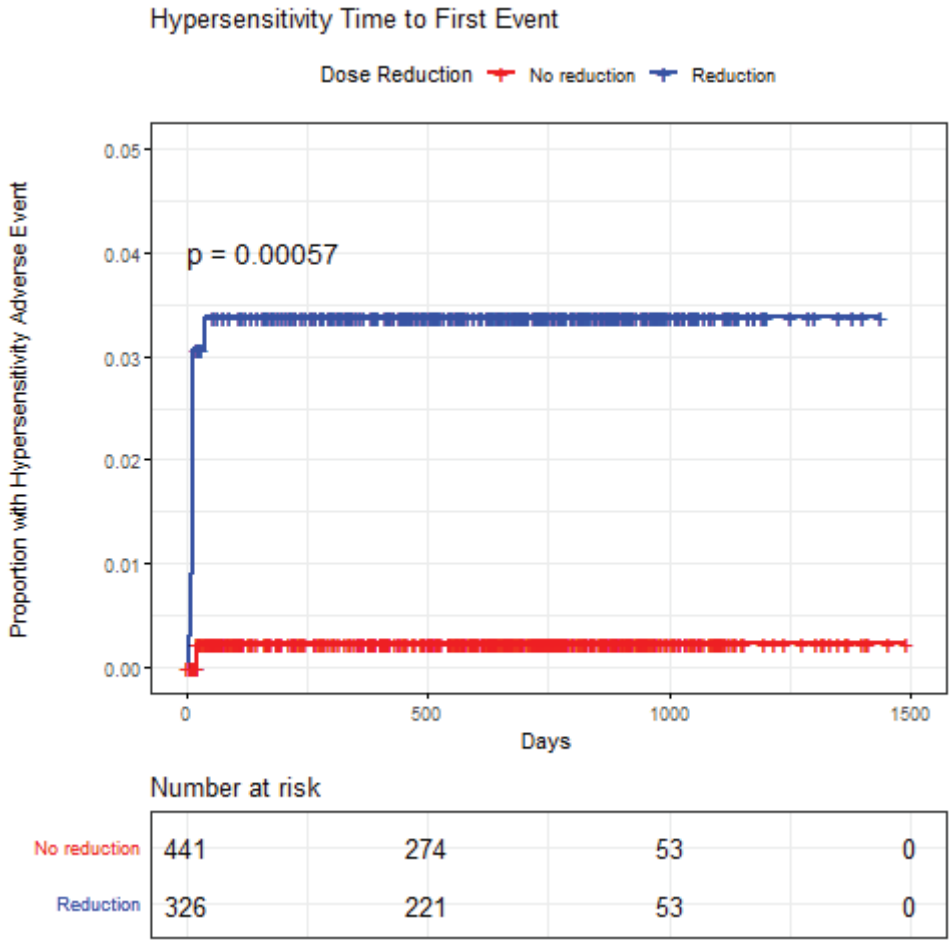
Source: Safety-ER-Analysis-04MAR2022.Rmd
Note: Quartile 1 includes the smallest selpercatinib AUCs, and Quartile 4 includes the largest selpercatinib AUCs (Table 19-17). Symbols represent time of censoring for subjects in that group.
Abbreviations: AE=adverse event; AUC=area under the plasma concentration-time curve

Figure 19-21. Kaplan-Meier Plot of Hypertension AE for All Subjects Stratified by Selpercatinib AUC Quartiles



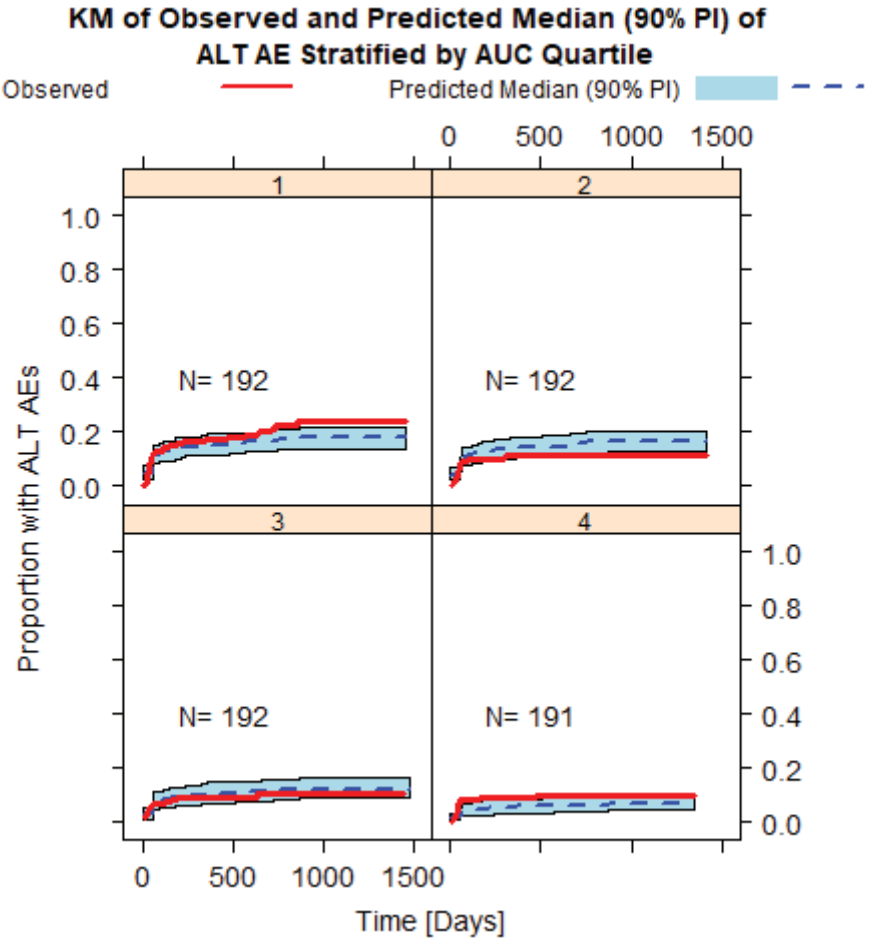
Source: Safety-ER-Analysis-04MAR2022.Rmd
Note: Symbols represent time of censoring for subjects in that group.
Abbreviations: AE=adverse event

Figure 19-22. Kaplan-Meier Plot of Hypertension AE for All Subjects Stratified by Selpercatinib Dose Reduction Status



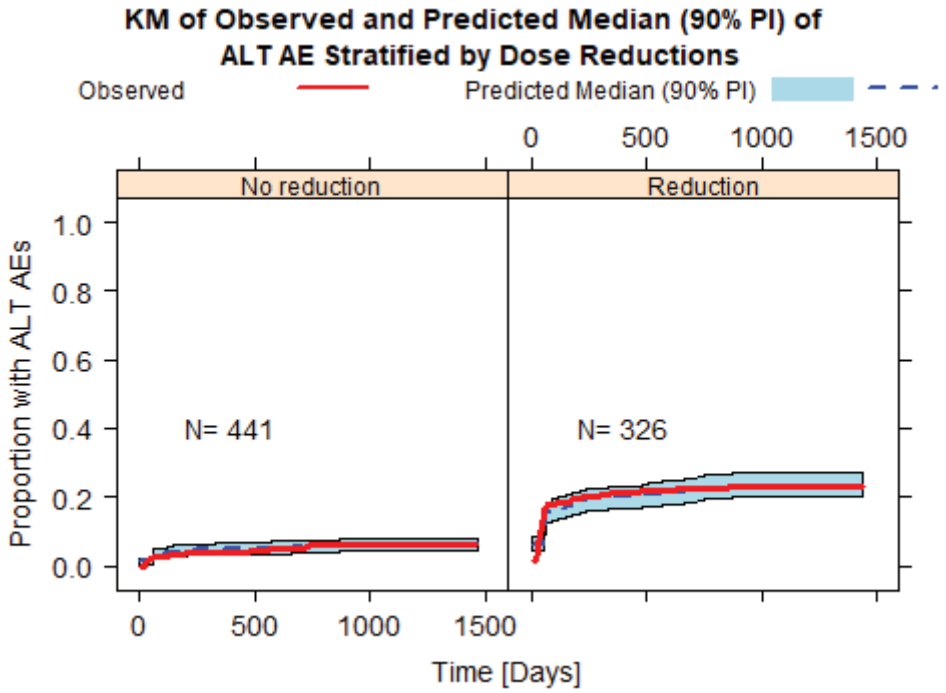
Source: Safety-ER-Analysis-04MAR2022.Rmd
Note: Symbols represent time of censoring for subjects in that group.
Abbreviations: AE=adverse event

Figure 19-23. Kaplan-Meier Plot of Hypersensitivity AE for All Subjects Stratified by Selpercatinib Dose Reduction Status



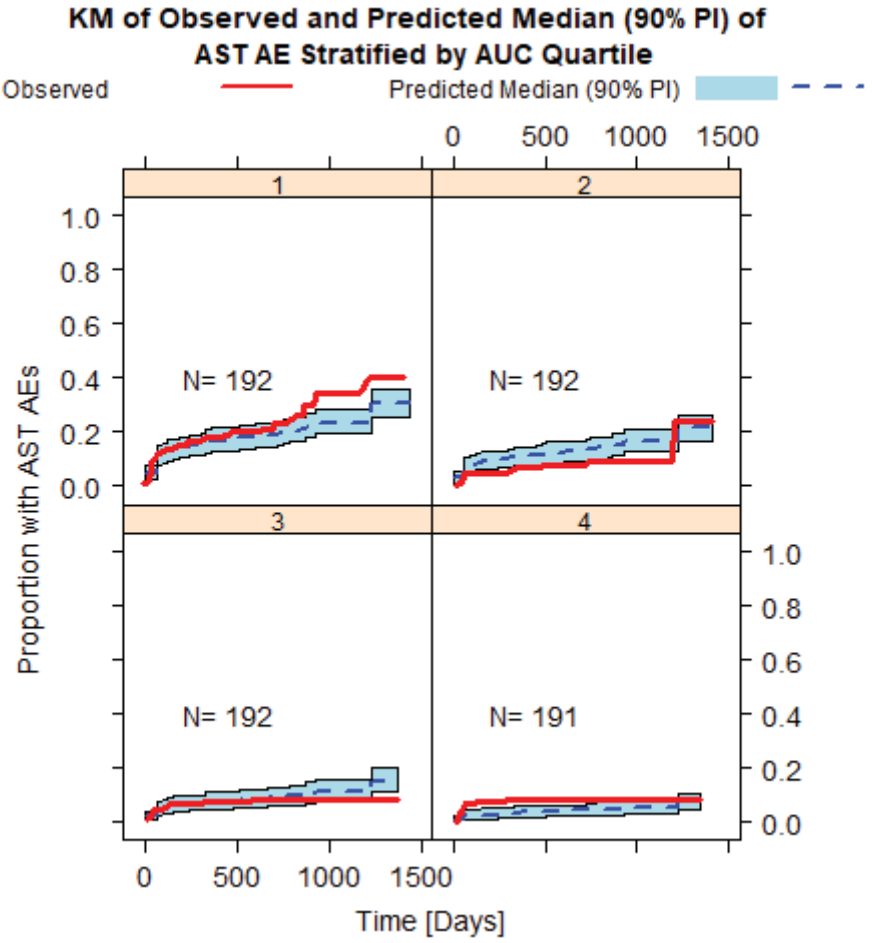
Source: Safety-ER-Analysis-04MAR2022.Rmd
Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AUC=area under the plasma concentration-time curve; KM=Kaplan-Meier; N=number of subjects; PI=prediction interval

Figure 19-24. Visual Predictive Check for the Final Time-to-Event Model for ALT AE With All Subjects Stratified by Selpercatinib AUC Quartile



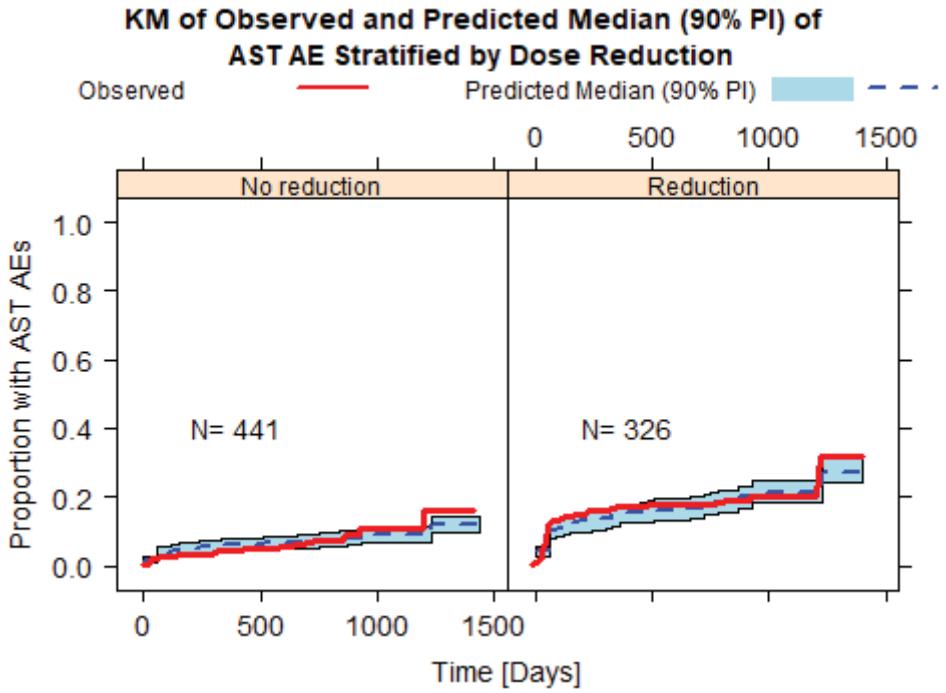
Source: Safety-ER-Analysis-04MAR2022.Rmd
Abbreviations: AE=adverse event; ALT=alanine aminotransferase; KM=Kaplan-Meier; N=number of subjects; PI=prediction interval

Figure 19-25. Visual Predictive Check for the Final Time-to-Event Model for ALT AE With All Subjects Stratified by Dose Reduction Status



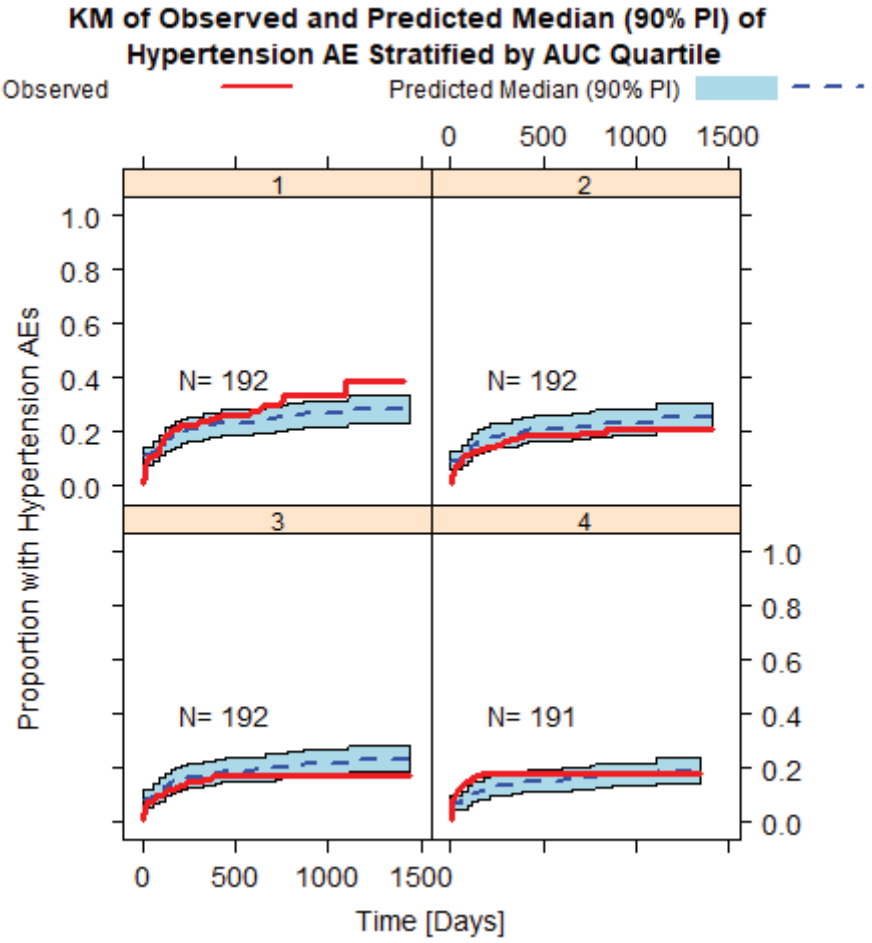
Source: Safety-ER-Analysis-04MAR2022.Rmd
Abbreviations: AE=adverse event; AST=aspartate aminotransferase; AUC=area under the plasma concentration-time curve; KM=Kaplan-Meier; N=number of subjects; PI=prediction interval

Figure 19-26. Visual Predictive Check for the Final Time-to-Event Model for AST AE With All Subjects Stratified by Selpercatinib AUC Quartile



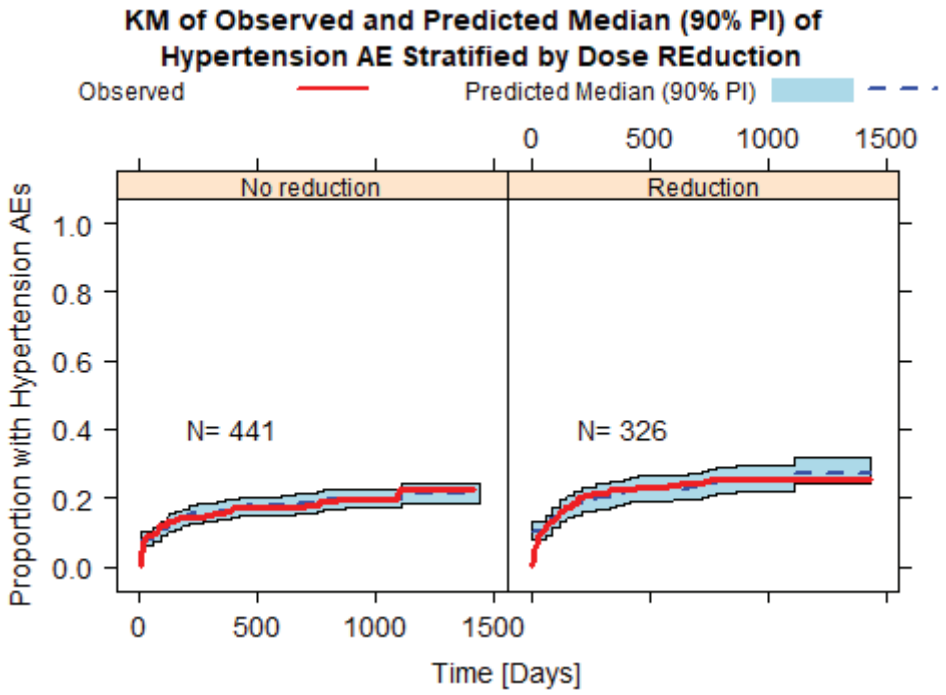
Source: Safety-ER-Analysis-04MAR2022.Rmd
Abbreviations: AE=adverse event; AST=aspartate aminotransferase; KM=Kaplan-Meier; N=number of subjects; PI=prediction interval

Figure 19-27. Visual Predictive Check for the Final Time-to-Event Model for AST AE With All Subjects Stratified by Dose Reduction Status



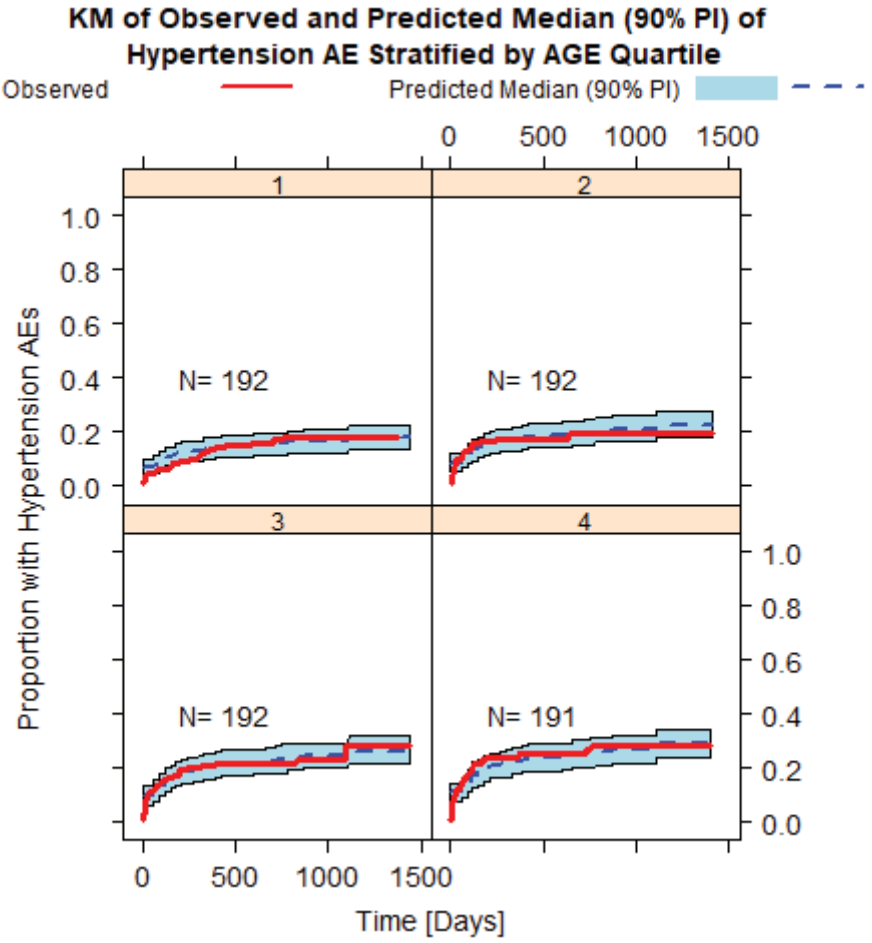
Source: Safety-ER-Analysis-04MAR2022.Rmd
Abbreviations: AE=adverse event; AUC=area under the plasma concentration-time curve; KM=Kaplan-Meier; N=number of subjects; PI=prediction interval

Figure 19-28. Visual Predictive Check for the Final Time-to-Event Model for Hypertension AE With All Subjects Stratified by Selpercatinib AUC Quartile



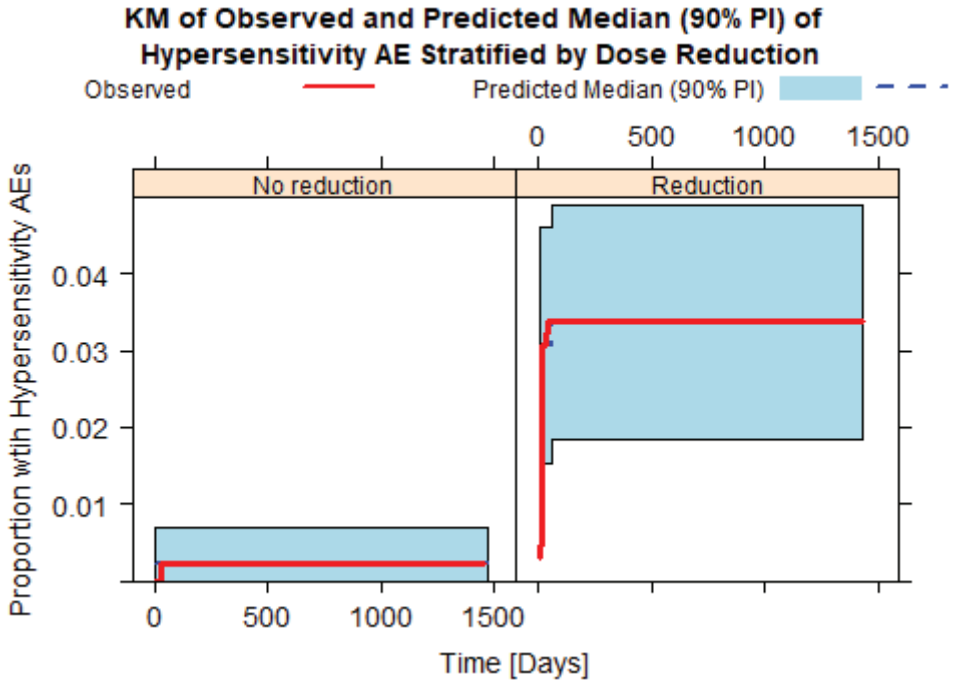
Source: Safety-ER-Analysis-04MAR2022.Rmd
Abbreviations: AE=adverse event; KM=Kaplan-Meier; N=number of subjects; PI=prediction interval

Figure 19-29. Visual Predictive Check for the Final Time-to-Event Model for Hypertension AE With All Subjects Stratified by Dose Reduction Status



Source: Safety-ER-Analysis-04MAR2022.Rmd
Abbreviations: AE=adverse event; KM=Kaplan-Meier; N=number of subjects; PI=prediction interval

Figure 19-30. Visual Predictive Check for the Final Time-to-Event Model for Hypertension AE With All Subjects Stratified by Age



Source: Safety-ER-Analysis-04MAR2022.Rmd
Abbreviations: AE=adverse event; KM=Kaplan-Meier; PI=prediction interval

Figure 19-31. Visual Predictive Check for the Final Time-to-Event Model for Hypersensitivity AE With All Subjects Stratified by Dose Reduction Status

The FDA's Assessment:

The ER analyses for AEs (increases in ALT, increases in AST, hypersensitivity, and hypertension) with selpercatinib were acceptable.

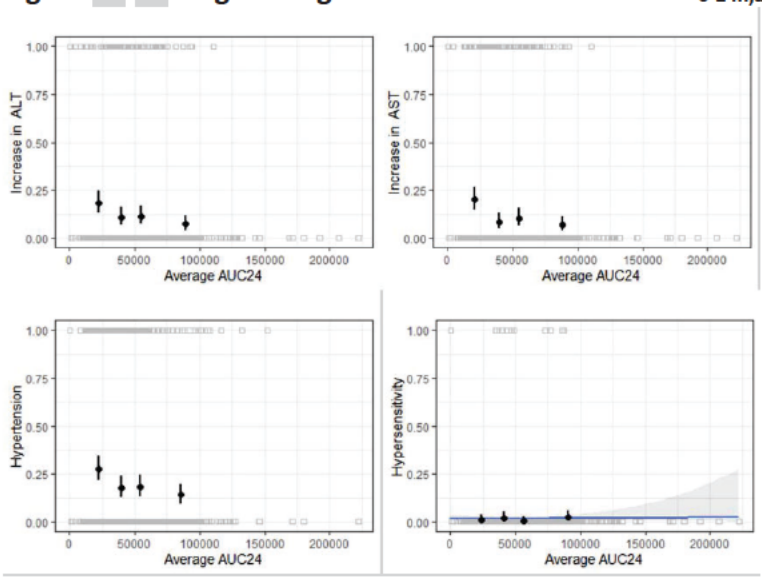
19.4.2.5. *ER Review Issues*

N/A

19.4.2.6. *Reviewer's Independent Analysis*

Independent ER analyses were conducted for selected AEs (increases in ALT, increases in AST, hypersensitivity, and hypertension). For patients with AE, the exposure metrics were selected as the average $AUC_{0\text{-}24h}$ from the start of treatment to the time of most recent incident of AEs. For the patients without AEs, the average $AUC_{0\text{-}24h}$ of the whole treatment were selected for the patients. Similar results were observed to the Applicant's analyses; none of the selected AEs show an increased risk as selpercatinib dose or exposure increased (**Figure 19-32**).

Figure 19-32: Logistic regressions for AEs versus $AUC_{0\text{-}24h,avg}$



Source: Reviewer's analysis

19.4.2.7. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

In this subgroup of patients, the exposure-response analyses for efficacy or for AEs of interest did not identify any treatment-related predictors. Overall, the totality of data from LIBRETTO-001 demonstrates a favorable benefit-risk profile.

The FDA's Assessment:

No clear ER relationships for efficacy or safety were identified. Due to the small sample size of the analysis, the result of the ER analysis for efficacy is inconclusive.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Laure Price, PharmD	CDER/OTS/OCP/DCPII	Sections: 6	**Select one:** __X__ Authored ___ Approved
	Signature: Lauren Price -S Digitally signed by Lauren Price -S Date: 2022.09.20 11:48:12 -04'00'			
Genomics Reviewer	Jeffery Kraft, PhD	CDER/OTS/OCP/DTPM	Sections: 6	**Select one:** _X__ Authored _____ Approved
	Signature: Jeffrey B. Kraft Jr -S Digitally signed by Jeffrey B. Kraft Jr -S Date: 2022.09.20 15:15:48 -04'00'			
Clinical Pharmacology Team Leader	Jeanne Fourie Zirkelbach, PhD	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	**Select one:** ___ Authored _____X Approved
	Signature: Jeanne Fourie Zirkelbach -S Digitally signed by Jeanne Fourie Zirkelbach -S Date: 2022.09.20 13:45:56 -04'00'			
Genomics Team Leader	Sarah Dorff, PhD	CDER/OTS/OCP/DTPM	Sections: 6	**Select one:** ___ Authored _X__ Approved
	Signature: Sarah E. Dorff -S Digitally signed by Sarah E. Dorff -S Date: 2022.09.20 13:08:19 -04'00'			
Division of Pharmacometrics (DPM) Reviewer	Yangbing Li, PhD	CDER/OTS/OCP/DPM	Sections: 6, 19.4	**Select one:** ___ Authored _____ Approved
	Signature: Yangbing Li -S (Affiliate) Digitally signed by Yangbing Li -S (Affiliate) Date: 2022.09.20 14:01:28 -04'00'			
Division of Pharmacometrics (DPM) Team Leader	Youwei Bi, PhD	CDER/OTS/OCP/DPM	Sections: 6, 19.4	**Select one:** ___ Authored _____Approved
	Signature: Youwei Bi -S Digitally signed by Youwei Bi -S Date: 2022.09.20 13:56:16 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Clinical Pharmacology Division Director	Stacy S Shord, PharmD	CDER/OTS/OCP/DCP II	Sections: 6, 19.4	**Select one:** ___ Authored X Approved
	Signature: Stacy Shord -S Digitally signed by Stacy Shord -S Date: 2022.09.19 15:25:11 -04'00'			
Clinical Reviewer	Elizabeth Duke, MD	CDER/OOD/DO2	Sections: 1-4 and 7-13	**Select one:** __X__ Authored ___ Approved
	Signature: Elizabeth Duke -S Digitally signed by Elizabeth Duke -S Date: 2022.09.19 15:19:20 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Diana Bradford, MD	CDER/OOD/DO2	Sections: see CTDL	**Select one:** ___ Authored ___ Approved
	Signature: see CDTL signature			
Statistical Reviewer	Michelle Marcovitz, PhD	CDER/OTS/DBV	Sections: 8.1, 8.3	**Select one:** _x_ Authored ___ Approved
	Signature: Michelle S. Marcovitz -S Digitally signed by Michelle S. Marcovitz -S Date: 2022.09.21 09:38:16 -04'00'			
Statistical Team Leader (Acting)	Anup Amatya, PhD	CDER/OTS/DBV	Sections: 8.1, 8.3	**Select one:** _x_ Authored _x_ Approved
	Signature: Anup K. Amatya -S Digitally signed by Anup K. Amatya -S Date: 2022.09.20 14:09:36 -04'00'			
Supervisory Mathematical Statistician (OB/DBV)	Pallavi Mishra-Kalyani, PhD	CDER/OTS/DBV	Sections: 8.1, 8.3	**Select one:** ___ Authored _x_ Approved
	Signature: Pallavi S. Mishra-kalyani -S Digitally signed by Pallavi S. Mishra-kalyani -S Date: 2022.09.20 07:47:05 -04'00'			
Associate Director for Labeling (ADL)	Barbara Scepura,	CDER/OOD	Sections: 11	**Select one:** _x_ Authored ___ Approved
	Signature: Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S Date: 2022.09.20 12:55:56 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Diana Bradford, MD	CDER/OOD/DO2	Sections: All	**Select one:** ___X Authored ___X Approved
	Signature: see DARRTS electronic signature			
Deputy Division Director (Clinical)	Harpreet Singh, MD	CDER/OOD/DO2	Sections: All	**Select one:** ___ Authored _X_ Approved

	Signature: see DARRTS electronic signature			

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213246Orig1s008

OTHER REVIEW(S)

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	September 20, 2022
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 213246/S-08
Product Name, Dosage Form, and Strength:	Retevmo (selpercatinib) capsules, 40 mg, 80 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eli Lilly and Company
FDA Received Date:	May 31, 2022, September 16, 2022, and September 19, 2022
TTT ID #:	2022-1281
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

Eli Lilly and Company submitted an efficacy supplement for Retevmo (selpercatinib) capsules to support accelerated approval for the following proposed indication:

(b) (4)

Subsequently, the Division of Oncology 2 (DO2) requested that we review the proposed Retevmo prescribing information (PI), container labels, and carton labeling and Patient Package Insert for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
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 evaluated the proposed changes to PI and patient information. We note the addition of the newly proposed solid tumor indication to Section 2.1 of the PI and the language added to the PPI pertaining to the new indication. We find these change acceptable from a medication error standpoint.

Further, we note there were no proposed changes to Section 3 Dosage Forms and Strengths, Section 16 How Supplied/Storage and Handling, or Section 17 Patient Counseling Information, nor were there any proposed changes to the container labels

4 CONCLUSION & RECOMMENDATIONS

The proposed Retevmo PI and PPI are acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Retevmo received on September 19, 2022 from Eli Lilly and Company.

Table 2. Relevant Product Information for Retevmo	
Initial Approval Date	May 8, 2020
Active Ingredient	selpercatinib
Indication	RET Fusion-Positive Non-Small Cell Lung Cancer; RET-Mutant Medullary Thyroid Cancer; RET Fusion-Positive Thyroid Cancer ***Proposed:*** (b) (4)
Route of Administration	Oral
Dosage Form	capsules
Strength	40 mg, 80 mg
Dose and Frequency	In adults and pediatric patients 12 years of age or older is based on weight : -Less than 50 kg: 120 mg orally twice daily -50 kg or greater: 160 mg orally twice daily
How Supplied	40 mg – bottles of 60 capsules 80 mg – bottles of 60 capsules
Storage	40 mg: Gray opaque, imprinted with “Lilly”, “3977” and “40 mg” in black ink-60 count bottle 80 mg: Blue opaque, imprinted with “Lilly”, “2980” and “80 mg” in black ink- 60 count bottle, 120 count bottle
Container Closure	White, HDPE bottles with closures containing an aluminum foil induction heat seal liner (polyethylene product contact layer) and HDPE (b) (4) closures.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 20, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Retevmo. Our search identified 3 previous reviews[a,b.c], and we considered our previous recommendations to see if they are applicable for this current review.

[a] Mahmoud, S. Label and Labeling Review for Retevmo (selpercatinib) (NDA 213246). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 MAY 18. RCM No.: 2021-31

[b] Stewart, J. Label and Labeling Review for Retevmo (selpercatinib) (NDA 213246). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 15. RCM No.: 2019-2472-1

[c] Stewart, J. Label and Labeling Review for Retevmo (selpercatinib) (NDA 213246). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 02. RCM No.: 2019-2472

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 Retevmo labels and labeling submitted by Eli Lilly and Company.

- Container label received on May 31, 2022
- Prescribing Information (Image not shown) received on September 19, 2022, available from \\CDSESUB1\EVSPROD\nda213246\0654\m1\us\proposed-uspi-clean.docx
- Patient Package Insert received on September 19, 2022, available from \\CDSESUB1\EVSPROD\nda213246\0654\m1\us\proposed-ppi-clean.docx

G.2 Label and Labeling Images

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


NDC 0002-2980-60
60 capsules
Rx only
Retevmo™
(selpercatinib)
capsules
80 mg
Each capsule contains
80 mg selpercatinib
www.retevmo.com
Lilly
Do not use if inner seal is missing or broken.
Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F).
Recommended Dosage: See prescribing information.
(01)00300022980602
YL06AIDAM01
Keep out of reach of children.
Marketed by: Lilly USA, LLC
Indianapolis, IN 46285, USA
Product of Ireland
GTIN: 00300022980602
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: September 16, 2022

To: Maritsa Stephenson, Regulatory Project Manager, DO2

Barbara Scepura, Associate Director for Labeling

From: Mispa Ajua-Alemanji, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, Team Leader, OPDP

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

NDA: 213246, S-007 and S-008

Background:

In response to DO2's consult request dated March 2, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and Patient Package Insert (PPI) for supplements S-007 and S-008 for RETEVMO® (selpercatanib) capsules, for oral use. These supplements include the transition from accelerated to traditional approval for the non-small cell lung cancer NSCLC indication, major safety updates, and the addition of a tumor agnostic indication (under accelerated approval).

PI/PPI:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on September 14, 2022, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed on September 14, 2022.

Thank you for your consult. If you have any questions, please contact Mispa Ajua-Alemanji at Mispa.Ajua-Alemanji@fda.hhs.gov.

PI:

Section	Statement from Draft (if applicable)	OPDP Comment
HIGHLIGHTS OF PRESCRIBING INFORMATION: WARNINGS AND PRECAUTIONS	(b) (4)	OPDP notes that section 5.9 includes the following information: "Withhold, dose reduce, or permanently discontinue RETEVMO based on severity." OPDP recommends revising the Hypothyroidism section of the Highlights to include this information, consistent with the management recommendations included with the other warnings and precautions in the Highlights.
1.1 Indications and Usage	(b) (4)	As noted by OPDP in the labeling meetings, from a promotional perspective, we are concerned that the addition of "locally advanced" to this indication will be used to promote Retevmo for *all* patients with locally advanced RET fusion-positive non-small cell lung cancer, when, as discussed during labeling meetings, not all patients with locally advanced disease would be appropriate for treatment with Retevmo. However, we acknowledge DO2's rationale as expressed in the labeling meetings and we defer to the division.

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/s/

MISPA L AJUA-ALEMANJI
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 15, 2022
To:	Maritsa Stephenson, PharmD, BCPS Regulatory Project Manager **Division of Oncology II (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Mispa Ajua-Alemanji, PharmD 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
Supplement Number:	S-007 and S-008
Applicant:	Loxo Oncology Inc., a wholly owned subsidiary of Eli Lilly and Company

1 INTRODUCTION

On November 23, 2021, Loxo Oncology Inc., a wholly owned subsidiary of Eli Lilly and Company, submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved New Drug Application (NDA) 213246/S-007 for RETEVMO (selpercatinib) capsules. With this submission, the Applicant proposes to convert the current non-small cell lung cancer indication from accelerated approval to full approval and proposes to fulfill postmarketing requirements 3829-2 and 3829-9.

On May 31, 2022, the Applicant submitted a PAS – Efficacy to NDA 213246/S-008 to propose an additional indication for RETEVMO (selpercatinib) capsules, for the (b) (4)

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 March 2, 2022 for S-007 and June 13, 2022 for S-008, 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 November 23, 2021 and May 31, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 6, 2022 and September 14, 2022.
- Draft RETEVMO (selpercatinib) capsules Prescribing Information (PI) received on November 23, 2021 and May 31, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 6, 2022 and September 14, 2022.

3 REVIEW METHODS

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

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

In our collaborative review of the 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.

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