CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

213246Orig1s011

Trade Name:	**RETEVMO**
Generic or Proper Name:	(selpercatinib)
Sponsor:	ELI LILLY AND CO
Approval Date:	September 27, 2024

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 2 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 2 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 and pediatric patients 2 years of age and older 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

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213246Orig1s011

APPROVAL LETTER

NDA 213246/S-011
NDA 213246/S-013

SUPPLEMENT APPROVAL/
FULFILLMENT OF POSTMARKETING REQUIREMENTS

Loxo Oncology Inc., a wholly owned subsidiary of Eli Lilly and Company
Attention: Michael P. Roesner
Director, Global Regulatory Affairs - North America
Lily Corporate Center, Drop Code 2543
Indianapolis, IN 46285

Dear Michael P. Roesner:

Please refer to the following supplemental new drug applications (sNDA) listed below, and its amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Retevmo (selpercatinib) capsules:

- *Prior Approval sNDA 011*, dated and received on November 29, 2023, which provides for updates to the Retevmo (selpercatinib) U.S. Prescribing Information labeling to include interim efficacy and safety results from the LIBRETTO-431 study; and

- *Prior Approval sNDA 013*, dated and received on March 28, 2024, which provides for fulfillment of Postmarketing Requirements (PMRs) 3892-1 and 3892-6, and conversion from accelerated approval to traditional approval of Retevmo (selpercatinib) for the treatment of adult and pediatric patients 2 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.

APPROVAL & LABELING

We have completed our review of these applications, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

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 and 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).

SUBPART H FULFILLED

We approved sNDA 213246/S-013 under the regulations at 21 CFR 314 Subpart H for accelerated approval of new drugs for serious or life-threatening illnesses. Approval of this supplement fulfills your commitments made under 21 CFR 314.510.

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 these indications have orphan drug designation, you are

[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.

exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENTS

We have received your submission dated March 28, 2024, containing the final reports for the following postmarketing requirements listed in the May 8, 2020, and May 29, 2024, approval letters.

3829-1 Submit the final report including datasets from a multi-center, randomized trial comparing selpercatinib to physician's choice of approved therapies in patients with kinase inhibitor-naïve, progressive, advanced or metastatic RET-mutant medullary thyroid cancer to confirm clinical benefit of selpercatinib with progression-free survival as a key secondary end point- as assessed by blinded independent central review.

3829-6 Conduct a rodent carcinogenicity study in rats to evaluate the potential for carcinogenicity. Submit a carcinogenicity protocol for a Special ProtocolAssessment prior to initiating the study.

4639-1 Complete the primary analysis for a multi-center, randomized trial (LIBRETTO-531) comparing selpercatinib to physician's choice of approved therapies in patients with kinase inhibitor-naïve, progressive, advanced or metastatic RET-mutant medullary thyroid cancer intended to confirm clinical benefit of selpercatinib with progression-free survival as a primary endpoint as assessed by blinded independent central review.

We have reviewed your submission and conclude that the above requirements were fulfilled.

We remind you that there are postmarketing requirements listed in the May 8, 2020, and May 29, 2024, approval letters that are still open.

We remind you that accelerated approval PMRs 4639-2 and 4639-3 listed in the May 29, 2024, approval letter are still open. Pursuant to 21 CFR 314.510 (Subpart H), continued approval of the drug is contingent upon verification and description of clinical benefit and completion of the clinical trial for PMRs 4639-2 and 4639-3.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

For NDA 213246/S-013

4697-1 Complete survival follow-up of patients in the LIBRETTO-531 trial at 125 deaths or 6 years from randomization of the first patient, whichever occurs first, to further characterize the efficacy and clinical benefit of selpercatinib in patients with advanced or metastatic *RET* mutant medullary thyroid cancer who are naïve to tyrosine kinase inhibitors.

The timetable you submitted on August 23, 2024, states that you will conduct this study according to the following schedule:

Trial Completion:	03/2026
Final Report Submission:	09/2026

For NDA 213246/S-011

4714-1 Complete survival follow-up of patients in the LIBRETTO-431 trial at 175 deaths to further characterize the efficacy and clinical benefit of selpercatinib in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a *RET* gene fusion.

The timetable you submitted on September 26, 2024, states that you will conduct this study according to the following schedule:

Trial Completion:	09/2033
Final Report Submission:	03/2034

Submit clinical protocols to your IND 144696 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**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. 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]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

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).

REPORTING REQUIREMENTS

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

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, email Maritsa Stephenson, Regulatory Health Project Manager, at maritsa.stephenson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Nicole Drezner, M.D.
Deputy Director
Division of Oncology 2
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

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/

NICOLE L DREZNER
09/27/2024 12:25:04 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213246Orig1s011

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
RETEVMO® (selpercatinib) tablets, for oral use

Initial U.S. Approval: 2020

---------- RECENT MAJOR CHANGES ----------

Indications and Usage	
RET-Mutant Medullary Thyroid Cancer (1.2)	09/2024
RET Fusion-Positive Thyroid Cancer (1.3)	06/2024
Other *RET* Fusion-Positive Solid Tumors (1.4)	05/2024
Dosage and Administration (2.3, 2.5, 2.6, 2.7)	05/2024
Warnings and Precautions (5.11)	05/2024

---------- 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 2 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 (1.2)
- Adult and pediatric patients 2 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) (1.3)
- Adult and pediatric patients 2 years of age and older 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[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)
- Adult and adolescent patients 12 years of age or older:

  the recommended dosage is based on weight (2.3):
  - Less than 50 kg: 120 mg orally twice daily
  - 50 kg or greater: 160 mg orally twice daily
- Pediatric patients 2 to less than 12 years of age:

the recommended dosage is based on body surface area (2.3):
  - 0.33 to 0.65 m^2: 40 mg orally three times daily
  - 0.66 to 1.08 m^2: 80 mg orally twice daily
  - 1.09 to 1.52 m^2: 120 mg orally twice daily
  - ≥1.53 m^2: 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)
- Tablets: 40 mg, 80 mg, 120 mg, 160 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 the 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 the 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 reduce the dose 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)
- *Slipped Capital Femoral Epiphysis/Slipped Upper Femoral Epiphysis (SCFE/SUFE) in Pediatric Patients:* Monitor patients for symptoms indicative of SCFE/SUFE and treat as medically and surgically appropriate (5.11, 6.1)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥25%) include:

- Adult patients with solid tumors: edema, diarrhea, fatigue, dry mouth, hypertension, abdominal pain, constipation, rash, nausea, and headache. (6)
- Pediatric patients with solid tumors: musculoskeletal pain, diarrhea, headache, nausea, vomiting, coronavirus infection, abdominal pain, fatigue, pyrexia, and hemorrhage. (6)

The most common Grade 3 or 4 laboratory abnormalities (≥5%) include:

- Adult patients with solid tumors: decreased lymphocytes, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), decreased sodium, and decreased calcium. (6)
- Pediatric patients with solid tumors: decreased calcium, decreased hemoglobin, and decreased neutrophils. (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 pediatric patients. Consider interrupting or discontinuing RETEVMO if abnormalities occur. (8.4)

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

Revised: 09/2024

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 2 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.

1.3 *RET* Fusion-Positive Thyroid Cancer

RETEVMO is indicated for the treatment of adult and pediatric patients 2 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).

1.4 Other *RET* Fusion-Positive Solid Tumors

RETEVMO is indicated for the treatment of adult and pediatric patients 2 years of age and older 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.

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 is not 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 is shown in Table 1:

Table 1: Recommended RETEVMO Dosage

Population	RETEVMO Dosage
Adult and adolescent patients 12 years of age or older based on body weight	
• Less than 50 kg	120 mg twice daily
• 50 kg or greater	160 mg twice daily
Pediatric patients 2 to less than 12 years of age based on body surface area	
• 0.33 to 0.65 m^2	40 mg three times daily
•	
• 0.66 to 1.08 m^2	80 mg twice daily
• 1.09 to 1.52 m^2	120 mg twice daily
• ≥1.53 m^2	160 mg twice daily
Dosing pediatric patients with body surface area less than 0.33 m^2 is not recommended	

Continue treatment with RETEVMO until disease progression or unacceptable toxicity.

Swallow the capsules whole. Do not crush or chew the capsules. Do not administer to pediatric patients who are unable to swallow a capsule.

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

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 2.

Table 2: Recommended RETEVMO Dose Reductions for Adverse Reactions

Current RETEVMO Dosage	Dose Reduction		
	First	Second	Third
40 mg three times daily	40 mg twice daily	40 mg once daily	permanently discontinue
80 mg twice daily	40 mg twice daily	40 mg once daily	permanently discontinue
120 mg twice daily	80 mg twice daily	40 mg twice daily	40 mg once daily
160 mg twice daily	120 mg twice daily	80 mg twice daily	40 mg twice daily
Permanently discontinue RETEVMO in patients unable to tolerate three dose reductions.			

The recommended dosage modifications for adverse reactions are provided in Table 3.

Table 3: 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 or permanently discontinue RETEVMO.
	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 4. 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 4: Recommended RETEVMO Dosage for Concomitant Use of Strong and Moderate CYP3A Inhibitors

	Recommended RETEVMO Dosage	
Current RETEVMO Dosage	**Moderate CYP3A Inhibitor**	**Strong CYP3A Inhibitor**
40 mg orally three times daily	40 mg orally once daily	40 mg orally once daily
80 mg orally twice daily	40 mg orally twice daily	40 mg orally twice daily
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 5 *[see Use in Specific Populations (8.7)]*.

Table 5: Recommended RETEVMO Dosage for Severe Hepatic Impairment

Current RETEVMO Dosage	**Recommended RETEVMO Dosage**
40 mg orally three times daily	40 mg orally twice daily
80 mg orally twice daily	40 mg orally twice daily
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.

Tablets:

- 40 mg: light gray, film coated, round tablet debossed with “Ret 40” on one side and “5340” on the other side.
- 80 mg: dark red-purple, film coated, round tablet debossed with “Ret 80” on one side and “6082” on the other side.
- 120 mg: light purple, film coated, round tablet debossed with “Ret 120” on one side and “6120” on the other side.
- 160 mg: light pink, film coated, round tablet debossed with “Ret 160” on one side and “5562” on the other side.

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 the 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 the 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 the 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 reduce the dose 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)]*.

5.11 Slipped Capital Femoral Epiphysis/Slipped Upper Femoral Epiphysis in Pediatric Patients

Slipped capital femoral epiphysis/slipped upper femoral epiphysis (SCFE/SUFE) occurred in 1 adolescent (3.7% of 27 patients) receiving RETEVMO in LIBRETTO-121 and 1 adolescent (0.5% of 193 patients) receiving RETEVMO in LIBRETTO-531 *[see Adverse Reactions (6.1)]*. Monitor patients for symptoms indicative of SCFE/SUFE and treat as medically and surgically appropriate *[see Adverse Reactions (6.1)]*.

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)]*
- Slipped Capital Femoral Epiphysis/Slipped Upper Femoral Epiphysis in Adolescent Patients *[see Warnings and Precautions (5.11)]*

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.

The safety population described in the WARNINGS and PRECAUTIONS and below reflects exposure to RETEVMO as a single agent administered at 160 mg orally twice daily evaluated in 796 patients with advanced solid tumors in LIBRETTO-001 *[see Clinical Studies (14)]*.

RET Gene Fusion or Gene Mutation Positive Solid Tumors

LIBRETTO-001

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, and 3% were Black or African American; and 5% were Hispanic/Latino. 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 6 summarizes the adverse reactions in LIBRETTO-001.

Table 6: Adverse Reactions (≥20%) in Patients Who Received RETEVMO in LIBRETTO-001

Adverse Reaction	**RETEVMO (n = 796)**	
	Grades 1-4[#] (%)	**Grades 3-4 (%)**
General Disorders and Administration Site Conditions		
Edema[1]	49	0.8*
Fatigue[2]	46	3.1*

Arthralgia	21	0.3*
Gastrointestinal Disorders		
Diarrhea[3]	47	5*
Dry Mouth	43	0
Abdominal pain[4]	34	2.5*
Constipation	33	0.8*
Nausea	31	1.1*
Vomiting	22	1.8*
Vascular Disorders		
Hypertension	41	20
Skin and Subcutaneous Tissue Disorders		
Rash[5]	33	0.6*
Nervous System Disorders		
Headache[6]	28	1.4*
Respiratory, Thoracic and Mediastinal Disorders		
Cough[7]	24	0
Dyspnea[8]	22	3.1
Blood and Lymphatic System Disorders		
Hemorrhage[9]	22	2.6
Investigations		
Prolonged QT interval	21	4.8*

1 Edema includes 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.

2 Fatigue includes asthenia and malaise.

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

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

5 Rash includes 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 sinus headache, tension headache.

7 Cough includes productive cough, upper airway cough syndrome.

8 Dyspnea includes dyspnea exertional, dyspnea at rest.

9 Hemorrhage includes, 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%); pneumonia (11%), hypersensitivity (6%); interstitial lung disease/pneumonitis, chylothorax, chylous ascites or tumor lysis syndrome (all < 2%).

Table 7 summarizes the laboratory abnormalities in LIBRETTO-001.

Table 7: 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

LIBRETTO-121

The safety population described below reflects exposure to RETEVMO as a single agent at 92 mg/m^2 orally twice daily evaluated in 27 patients with advanced solid tumors harboring an activating *RET* alteration in LIBRETTO-121 *[see Clinical Studies (14)]*. Among the 27 pediatric and adolescent patients who received RETEVMO, 81% were exposed for 6 months or longer and 59% were exposed for greater than one year.

The median age was 13 years (range: 2 to 20 years); 22% were pediatric patients 2 to 12 years of age; 59% were male; and 52% were White, 26% were Asian, and 11% were Black or African American; and 19% were Hispanic/Latino. The most common cancers were MTC (52%), and papillary thyroid cancer (37%).

Serious adverse reactions occurred in 22% of patients who received RETEVMO. The serious adverse reactions (in 1 patient each) were abdominal infection, abdominal pain, aspiration, constipation, diarrhea, epiphysiolysis, nausea, pneumonia, pneumatosis intestinalis, rhinovirus infection, sepsis, vomiting.

Dosage interruptions due to an adverse reaction occurred in 22% of patients who received RETEVMO. Adverse reactions requiring dosage interruption in ≥5% of patients included decreased neutrophils.

Dose reductions due to an adverse reaction occurred in 15% of patients who received RETEVMO. Adverse reactions requiring dosage reductions in ≥2% of patients included decreased neutrophils, increased ALT, and increased weight.

The most common adverse reactions (≥25%) were musculoskeletal pain, diarrhea, headache, nausea, vomiting, coronavirus infection, abdominal pain, fatigue, pyrexia, and hemorrhage.

The most common Grade 3 or 4 laboratory abnormalities (≥5%) were decreased calcium, decreased hemoglobin, and decreased neutrophils.

Table 8 summarizes the adverse reactions in LIBRETTO-121.

Table 8: Adverse Reactions (≥15%) in Patients Who Received RETEVMO in LIBRETTO-121

Adverse Reactions	RETEVMO N= 27	
	Grades 1-4[#] %	Grades 3-4 %
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[1]	56	0
Gastrointestinal disorders		
Diarrhea[2]	41	0
Nausea	30	3.7[*]
Vomiting	30	7*
Abdominal pain[3]	26	0
Constipation	19	7[*]
Stomatitis[4]	15	0
Nervous System Disorders		
Headache	33	0
Infections and Infestations		
Coronavirus infection	30	0
Upper respiratory tract infection	22	0
General Disorders and Administration Site Conditions		
Fatigue[5]	26	0
Pyrexia	26	0
Edema[6]	19	0
Increased weight	19	7*
Blood and Lymphatic System Disorders		
Hemorrhage[7]	26	3.7*
Respiratory, Thoracic and Mediastinal Disorders		
Oropharyngeal pain	22	0
Cough	22	0
Endocrine Disorders		
Hypothyroidism[8]	19	0
Skin and Subcutaneous Tissue Disorders		
Rash[9]	19	0
Renal and Urinary Disorders		
Proteinuria	15	0

1 Musculoskeletal pain includes arthralgia, back pain, bone pain, musculoskeletal chest pain, non-cardiac chest pain, neck pain, pain in extremity

2 Diarrhea includes anal incontinence

3 Abdominal pain includes abdominal pain upper

4 Stomatitis includes angular cheilitis

5 Fatigue includes asthenia and malaise

6 Edema includes edema peripheral, face edema, localized edema, generalized edema, swelling

7 Hemorrhage includes mouth hemorrhage, epistaxis

8 Hypothyroidism includes blood thyroid stimulating hormone increased, thyroglobulin increased

9 Rash includes rash maculopapular

* No Grade 4 events were reported.

[#] Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

Clinically relevant adverse reactions in <15% of patients who received RETEVMO include dizziness (11%), urinary tract infection (11%), decreased appetite (7%), electrocardiogram QT prolonged (7%), hypersensitivity (7%), hypertension (7%), and pneumonia (3.7%).

Table 9 summarizes the laboratory abnormalities in LIBRETTO-121.

Table 9: Select Laboratory Abnormalities (≥15%) Worsening from Baseline in Patients Who Received RETEVMO in LIBRETTO-121

	RETEVMO[1]	
Laboratory Abnormality	**Grades 1-4[#] (%)**	**Grades 3-4 (%)**
Chemistry		
Decreased calcium	59	7
Increased ALT	56	3.7*
Increased alkaline phosphatase	52	0
Increased AST	48	3.7*
Decreased albumin	44	0
Increased bilirubin	30	0
Increased creatinine	22	0
Decreased potassium	22	3.7
Decreased magnesium	15	3.7
Hematology		
Decreased neutrophils	44	7*
Decreased lymphocytes	24	4.8
Decreased platelets	22	0
Decreased hemoglobin	19	7*

[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 21 to 27 patients.

* No Grade 4 abnormalities were reported.

[#] Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.

Treatment-naïve RET Fusion-Positive Non-small Cell Lung Cancer

LIBRETTO-431

The safety population described below reflects exposure to RETEVMO as a single agent administered at 160 mg orally twice daily evaluated in 158 patients with unresectable locally advanced or metastatic *RET* fusion-positive NSCLC in LIBRETTO-431 [see Clinical Studies (14)]. Among the 158 patients who received RETEVMO, the median duration of exposure was 16.7 months (range: 5 days to 37.9 months); 87% were exposed for 6 months or longer and 70% were exposed for one year or longer.

The median age was 61 years (range: 31 to 87 years); 46% were male; and 36% were White, 58% were Asian, 1.3% were Black or African American, 1.3% were American Indian or Alaska Native, and 3.2% were missing.

Serious adverse reactions occurred in 35% of patients who received RETEVMO. The most frequent serious adverse reactions (≥2% of patients) were pleural effusion, and abnormal hepatic function. Fatal adverse reactions occurred in 4.4% of patients who received RETEVMO; fatal adverse reactions included myocardial infarction (n = 2), respiratory failure (n = 2), cardiac arrest, malnutrition, and sudden death (n = 1, each).

Permanent discontinuation due to an adverse reaction occurred in 10% of patients who received RETEVMO. Adverse reactions resulting in permanent discontinuation in ≥1% of patients included increased ALT (1.3%), and myocardial infarction (1.3%).

Dosage interruptions due to an adverse reaction occurred in 72% of patients who received RETEVMO. Adverse reactions requiring dosage interruption in ≥5% of patients included increased ALT, hypertension, increased AST, QT prolongation, diarrhea, and COVID-19 infection.

Dose reductions due to an adverse reaction occurred in 51% of patients who received RETEVMO. Adverse reactions requiring dose reductions in ≥5% of patients included increased ALT, increased AST, QT prolongation.

The most common adverse reactions (≥25%) in patients who received RETEVMO were hypertension, diarrhea, edema, dry mouth, rash, fatigue, abdominal pain, and musculoskeletal pain.

The most common Grade 3 or 4 laboratory abnormalities (≥5%) in patients who received RETEVMO were increased ALT, increased AST, and decreased lymphocytes.

Table 10 summarizes the adverse reactions in LIBRETTO-431.

Table 10: Adverse Reactions (≥15%) in Patients on Either Arm in LIBRETTO-431

Adverse Reaction	RETEVMO (n=158)		Chemotherapy with or without pembrolizumab (n=98)	
	Grades 1-4# (%)	Grades 3-4 (%)	Grades 1-4# (%)	Grades 3-4 (%)
Vascular disorders				
Hypertension	48	20*	7	3.1*
Gastrointestinal disorders				
Diarrhea[1]	44	1.3*	24	2.0*
Dry mouth[2]	39	0	6	0
Abdominal pain[3]	25	0.6*	19	2.0*
Constipation	22	0	40	1.0*
Stomatitis[4]	18	0	16	0
Nausea	13	0	44	1.0*
Vomiting[5]	13	0	23	1.0*
General disorders and administration site conditions				
Edema[6]	41	2.5*	28	0
Fatigue[7]	32	3.2*	50	5*
Pyrexia	13	0.6*	23	0
Skin and subcutaneous tissue disorders				
Rash[8]	33	1.9*	30	1.0*
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[9]	25	0	28	0
Investigations				
Electrocardiogram QT prolonged	20	9*	1.0	0
Infections and infestations				
COVID-19 infection	19	0.6*	18	0
Metabolism and nutrition disorders				
Decreased appetite	17	0	34	2.0*

[1] Diarrhea includes diarrhea, anal incontinence.

[2] Dry mouth includes dry mouth, mucosal dryness.

[3] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, gastrointestinal pain.

[4] Stomatitis includes stomatitis, mouth ulceration, mucosal inflammation.

[5] Vomiting includes vomiting, retching, regurgitation.

[6] Edema includes edema, edema peripheral, face edema, periorbital edema, swelling face, peripheral swelling, localized edema, eyelid edema, orbital edema, eye edema, scrotal edema, penile edema, orbital swelling, periorbital swelling.

[7] Fatigue includes fatigue, asthenia, malaise.

[8] Rash includes rash, rash maculopapular, skin exfoliation, rash erythematous, rash macular, dermatitis, urticaria, rash papular, dermatitis allergic, rash pustular, rash vesicular, genital rash.

[9] Musculoskeletal pain includes musculoskeletal pain, arthralgia, back pain, bone pain, musculoskeletal chest pain, non-cardiac chest pain, neck pain, pain in extremity.

* No Grade 4 abnormalities were reported.

Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

Clinically relevant adverse reactions in <15% of patients who received RETEVMO include headache (14%); hemorrhage (13%); urinary tract infections (12%); hypothyroidism (9%); pneumonia (9%); dizziness (8%); interstitial lung disease/pneumonitis (4.4%); hypersensitivity, chylous ascites, and chylothorax (all < 2%).

Table 11 summarizes the laboratory abnormalities in LIBRETTO-431.

Table 11: Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients on Either Arm in LIBRETTO-431

Laboratory Abnormality[1]	RETEVMO		Chemotherapy with or without pembrolizumab	
	Grades 1-4# (%)	Grades 3-4 (%)	Grades 1-4# (%)	Grades 3-4 (%)
Chemistry				
ALT increased	81	21	63	4.1
AST increased	77	10	46	0
Alkaline phosphatase Increased	35	1.3	22	0
Total bilirubin Increased	52	1.3	9	0
Blood creatinine Increased	23	0	21	0
Magnesium decreased	16	0.6	8	0
Albumin decreased	25	0	5	0
Calcium decreased	53	1.9	24	1.0
Sodium decreased	31	3.2	41	2.1
Potassium decreased	17	1.3	15	1.0
Hematology				
Platelets decreased	53	3.2	39	5
Lymphocyte count decreased	53	8	64	15
Hemoglobin decreased	21	0	91	5
Neutrophil count decreased	53	2.0	58	11

[1] Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available: RETEVMO (range: 154 to 157 patients) and chemotherapy with or without pembrolizumab (range: 96 to 97 patients).

Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

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)]*.

RET-Mutant Medullary Thyroid Cancer

LIBRETTO-531

The safety population described below reflects exposure to RETEVMO as a single agent administered at 160 mg (adults) or at 92 mg/m^2 (adolescent, not to exceed 160 mg) orally twice daily, in patients with progressive, advanced, kinase inhibitor naïve, *RET*-mutant medullary thyroid cancer in LIBRETTO-531 *[see Clinical Studies (14.2)].* Among the 193 patients who received RETEVMO, the observed median duration of exposure was 14.5 months (range: 25 days to 36 months); 80% were exposed for 6 months or longer and 59% were exposed for one year or longer.

The median age was 55 years (range: 12 to 84 years); 63% were male; and 69% were White, 28% were Asian, 2.9% were Black or African American and ethnicity was not routinely collected.

Serious adverse reactions occurred in 22% of patients who received RETEVMO. The most frequent serious adverse reactions were pneumonia and pyrexia (n = 3, each) and hypertension and urinary tract infection (n = 2, each). Fatal adverse reactions occurred in 2.1% of patients; fatal adverse reactions included COVID-19, diabetic ketoacidosis, multiple organ dysfunction syndrome, and sudden death (n=1 each).

Permanent discontinuation due to an adverse reaction occurred in 4.7% of patients who received RETEVMO. Adverse reactions resulting in permanent discontinuation were edema, multiple organ dysfunction syndrome, sudden death, AST increased, diabetic ketoacidosis, chronic kidney disease, retinopathy, COVID-19, and somatic symptom disorder (n = 1, each).

Dosage interruptions due to an adverse reaction occurred in 49% of patients who received RETEVMO. Adverse reactions requiring dosage omission in ≥5% of patients included ALT increased (9%) and hypertension (7%).

Dose reductions due to an adverse reaction occurred in 39% of patients who received RETEVMO. One adverse reaction, increased ALT (7%), required a dose reduction in ≥5% of patients.

The most common adverse reactions (≥25%) in patients who received RETEVMO were hypertension, edema, dry mouth, fatigue, and diarrhea.

The most common Grade 3 or 4 laboratory abnormalities (≥5%) in patients who received RETEVMO were decreased lymphocytes, increased ALT, decreased neutrophils, increased ALP, increased blood creatinine, decreased calcium, and increased AST.

Table 12 summarizes the adverse reactions in LIBRETTO-531.

Table 12: Adverse Reactions (≥10%) in Patients Who Received RETEVMO in LIBRETTO-531

Adverse Reaction	RETEVMO N = 193		Cabozantinib or Vandetanib N = 97	
	Grades 1-4[#] (%)	Grades 3-4 (%)	Grades 1-4[#] (%)	Grades 3-4 (%)
Vascular disorders				
Hypertension[1]	43	19*	41	18*
General disorders and administration-site conditions				
Edema[2]	33	0	5	0
Fatigue[3]	28	4.1*	47	9*
Pyrexia	12	1.0*	2.1	0
Gastrointestinal disorders				
Dry mouth[4]	32	0.5*	10	1.0*

Diarrhea[5]	26	3.1*	61	8*
Abdominal pain[6]	18	0.5*	21	2.1*
Constipation	16	0	12	0
Stomatitis[7]	14	0.5*	42	13*
Pyrexia	12	1.0*	2.1	0
Nausea	10	1.0*	32	5*
Nervous system disorders				
Headache[8]	23	0.5*	21	0
Skin and subcutaneous tissue disorders				
Rash[9]	19	1.6*	27	4.1*
Reproductive system and breast disorders				
Erectile dysfunction	16	0	0	0
Investigations				
Electrocardiogram QT prolonged[10]	14	4.7*	13	2.1*
Metabolism and nutrition disorders				
Decreased appetite	12	0.5*	28	5*
Endocrine disorders				
Hypothyroidism[11]	11	0	21	0

1 Hypertension includes hypertension, blood pressure increased.

2 Edema includes edema peripheral, face edema, periorbital edema, swelling face, peripheral swelling, localized edema, eyelid edema, generalized edema, eye swelling, lymphoedema, orbital edema, eye edema, edema, edema genital, swelling, scrotal edema, scrotal swelling, angioedema, skin edema, testicular swelling, vulvovaginal swelling.

3 Fatigue includes fatigue, asthenia, malaise.

4 Dry mouth includes dry mouth, mucosal dryness.

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

6 Abdominal pain included abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, gastrointestinal pain.

7 Stomatitis includes stomatitis, mouth ulceration, mucosal inflammation.

8 Headache includes headache, sinus headache, tension headache.

9 Rash includes rash, rash maculopapular, skin exfoliation, rash erythematous, rash macular, dermatitis, urticaria, rash pruritic, exfoliative rash, rash papular, dermatitis allergic, rash follicular, rash generalized, rash pustular, butterfly rash, rash morbilliform, rash vesicular.

10 Electrocardiogram QT prolongation includes electrocardiogram QT prolonged, electrocardiogram QT interval abnormal.

11 Hypothyroidism includes hypothyroidism, blood thyroid stimulating hormone increased.

* Only includes a Grade 3 adverse reaction

\# Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0.

Clinically relevant adverse reactions in ≤10% of patients who received RETEVMO include dizziness (8%); urinary tract infections (8%); vomiting (8%); pneumonia, interstitial lung disease/pneumonitis, chylous ascites and hypersensitivity (all < 2%).

Table 13 summarizes the laboratory abnormalities in LIBRETTO-531.

Table 13: Select Laboratory Abnormalities (≥5%) Worsening from Baseline in Patients Who Received RETEVMO in LIBRETTO-531

Laboratory Abnormality	RETEVMO[1]		Cabozantinib or Vandetanib[1]	
	Grades 1-4[#] %	Grades 3-4 %	Grades 1-4[#] %	Grades 3-4 %
Chemistry				
Calcium decreased	55	5	62	11
ALT increased	53	16	72	7*
AST increased	47	5	68	3.2*
Alkaline phosphatase increased	37	6	28	5
Total bilirubin increased	32	1.1	30	3.2*
Blood creatinine increased	27	6	16	8
Sodium decreased	20	3.2*	16	0
Albumin decreased	11	1.1	7	0
Magnesium decreased	9	3.3	26	9
Potassium decreased	8	0	22	4.4*
Hematology				
Lymphocyte count decreased	41	18	36	13
Neutrophil count decreased	33	14	42	19
Platelets decreased	28	1.1	34	1.1*
Hemoglobin decreased	18	2.1*	23	2.1*

1 Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available: RETEVMO (range: 183 to 191 patients) and chemotherapy with or without cabozantinib or vandetanib (range: 91 to 94 patients).

* Only includes a Grade 3 laboratory abnormality

\# Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0

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 2 years of age and older for the treatment of:

- advanced or metastatic medullary thyroid cancer (MTC) with a *RET* mutation who require systemic therapy
- advanced or metastatic thyroid cancer with a *RET* gene fusion who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate)
- 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.

Use of RETEVMO for these indications is supported by evidence from adequate and well-controlled studies in adult and pediatric patients with additional pharmacokinetic and safety data in pediatric patients 2 years of age and older *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.2, 14.3, 14.4)]*. The predicted exposures of selpercatinib in pediatric patients at the recommended dosages were within the range of values predicted in patients ≥ 12 years and ≥ 50 kg in body weight receiving the approved recommended dosage of 160 mg twice daily *[see Clinical Pharmacology (12.3)]*.

The safety and effectiveness of RETEVMO have not been established in these indications in patients less than 2 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 effect 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 pediatric 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

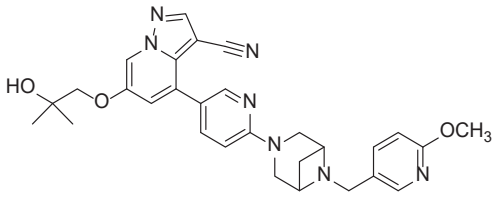
No dosage modification is recommended for patients with mild to severe renal impairment [estimated Glomerular Filtration Rate (eGFR) ≥15 to 89 mL/min, estimated by Modification of Diet in Renal Disease (MDRD) equation]. The recommended dosage has not been established for patients with end-stage renal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

RETEVMO contains selpercatinib, 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 capsules contain either 40 mg or 80 mg of selpercatinib in hard gelatin capsules for oral use. Each capsule contains inactive ingredients of colloidal silicon dioxide and microcrystalline cellulose. 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.

RETEVMO tablets contain 40 mg, 80 mg, 120 mg or 160 mg of selpercatinib as film coated, debossed tablets for oral use. Each tablet contains inactive ingredients of croscarmellose sodium, hydroxypropyl cellulose, mannitol, microcrystalline cellulose, and sodium stearyl fumarate. The tablet film coating material contains polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc. Additionally, the film coating of the 40 mg, 80 mg, and 120 mg tablets contains ferrosoferric oxide and the film coating of the 80 mg, 120 mg, and 160 mg tablets contain ferric oxide.

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 capsules were evaluated in patients with locally advanced or metastatic solid tumors administered 160 mg twice daily unless otherwise specified. The capsule and tablet dosage forms of selpercatinib are bioequivalent. 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 $AUC_{0\text{-}24h}$ 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

For both the capsule and tablet dosage forms 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 203 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 (9.6 kg to 179 kg).

No clinically significant differences in the pharmacokinetics of selpercatinib were observed based on age (2 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.

Pediatric patients

The exposures of selpercatinib in pediatric patients are predicted to be comparable to those in adult patients administered at the recommended dosages.

Patients with Hepatic Impairment

The selpercatinib $AUC_{0\text{-}INF}$ increased 1.07-fold, 1.32-fold, and 1.77-fold 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 14).

Table 14: 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 $AUC_{0\text{-}INF}$ 2.33-fold and C_{max} 1.3-fold.

Moderate CYP3A Inhibitors: Coadministration of multiple doses of diltiazem, fluconazole, or verapamil (moderate CYP3A inhibitors) is predicted to increase the selpercatinib AUC 1.6 to 1.99-fold and C_{max} 1.46 to 1.76-fold.

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 $AUC_{0\text{-}INF}$ 2.88-fold and C_{max} 1.91-fold.

CYP3A Substrates: Coadministration of RETEVMO with midazolam (sensitive CYP3A substrate) increased the midazolam $AUC_{0\text{-}INF}$ 1.54-fold and C_{max} 1.39-fold.

P-glycoprotein (P-gp) Substrates: Coadministration of RETEVMO with dabigatran (P-gp substrate) increased the dabigatran $AUC_{0\text{-}INF}$ 1.38-fold and C_{max} 1.43-fold.

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

Selpercatinib was not carcinogenic in a 2-year study in rats when administered by daily oral gavage at doses up to 20 mg/kg in males or 40 mg/kg in females (approximately equal to the human exposure by AUC at the 160 mg twice daily clinical dose). Selpercatinib was not carcinogenic in a 6-month study in rasH2 transgenic mice when administered by daily oral gavage at doses of up to 60 mg/kg.

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 160 twice daily clinical 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 clinical 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 clinical 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

LIBRETTO-001

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 or African American; 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-PD1/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 15.

Table 15: 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 or African American. 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 16.

Table 16: 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.

LIBRETTO-431

The efficacy of RETEVMO was evaluated in patients with unresectable, locally advanced or metastatic, *RET* fusion-positive NSCLC enrolled in a multicenter, open-label, active-controlled, randomized trial (LIBRETTO-431, NCT04194944). The trial evaluated RETEVMO compared to platinum-based and pemetrexed chemotherapy with or without pembrolizumab in patients with *RET* fusion-positive, unresectable locally advanced or metastatic NSCLC with no previous systemic therapy for metastatic disease.

Patients (N=261) were randomized to receive either RETEVMO (160 mg orally twice daily) in continuous 21-day cycles or pemetrexed intravenously (IV) (500 mg per square meter of body-surface area) along with the investigator's choice of platinum therapy (carboplatin IV [AUC 5, maximum dose 750 mg] or cisplatin IV [75 mg per square meter]) with or without pembrolizumab IV (200 mg) every 21 days. Treatment continued until disease progression or unacceptable toxicity. Crossover from the control arm to RETEVMO was permitted following disease progression. Patients were stratified according to geographic region (East Asia vs. elsewhere), brain metastases at baseline (presence vs. absence or unknown), and the investigator's intent (before randomization) to treat the patient with or without pembrolizumab. Tumor assessments were performed every 6 weeks for two assessments, then every 9 weeks for four assessments, and then every 12 weeks thereafter.

The major efficacy outcome measure was progression-free survival (PFS) in patients intended to be treated with chemotherapy in combination with pembrolizumab and in the overall study population as determined by a blinded independent review committee (BIRC) according to RECIST v1.1. Other efficacy outcome measures included overall survival (OS) and overall response rate (ORR).

A total of 212 patients were enrolled in LIBRETTO-431 with an intent to treat with pembrolizumab if randomized to the control arm (129 into RETEVMO arm and 83 into chemotherapy with pembrolizumab arm). The median age was 61.5 years (range: 31 to 84 years); 47% were male; 41% White, 55% Asian, and 0.9% Black or African American, 1.4% American Indian or Alaska Native, 1.9% were race not reported; ethnicity was not reported in 96% of patients. ECOG performance status was 0-1 (97%) or 2 (3%), 68% were never smokers, 93% of patients had metastatic disease, and 14% had measurable intracranial metastases at baseline, as determined by a neuroradiologic BIRC. RET fusions were detected in 60% of patients using NGS and 40% using PCR (89% tumor samples; 11% in blood).

Efficacy results from the pre-planned interim efficacy analysis are summarized in Table 17.

Table 17: Efficacy Results in LIBRETTO-431: RETEVMO versus Chemotherapy with Pembrolizumab

	RETEVMO (n = 129)	**Chemotherapy with pembrolizumab (n = 83)**
Progression-Free Survival		
Number (%) of patients with an event	49 (38%)	49 (59%)
Medians in months (95% CI)	24.8 (16.9, NE)	11.2 (8.8, 16.8)
Hazard ratio[1] (95% CI)	0.46 (0.31, 0.70)	
p-value[2]	0.0002	
Overall Response Rate (95% CI)	84% (76, 90)	65% (54, 75)
Complete response	7%	6%
Partial response	77%	59%
Duration of Response		

Median in months (95% CI) % with ≥ 12 months[3]	24.2 (17.9, NE) 60%	11.5 (9.7, 23.3) 30%

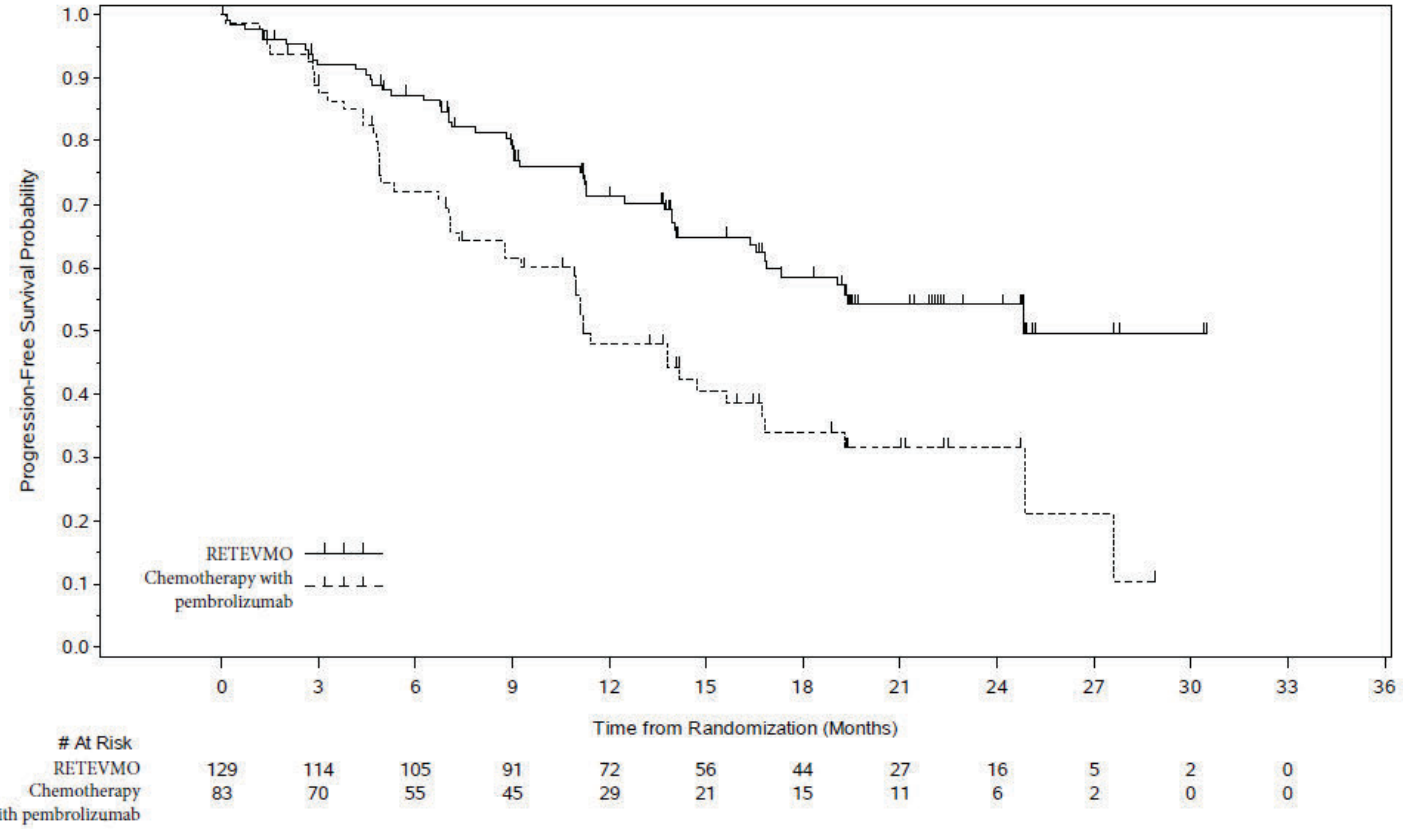
[1] Based on the stratified Cox proportional hazard model, stratified by geographic location (East Asia versus elsewhere), brain metastases at baseline according to investigator (presence versus absence or unknown).

[2] Based on stratified log-rank test, stratified by geographic location (East Asia versus elsewhere), brain metastases at baseline according to investigator (presence versus absence or unknown).

[3] Based on observed duration of response.

NE = not estimable

Figure 1: Kaplan-Meier Curves of Progression-Free Survival in LIBRETTO-431: RETEVMO versus Chemotherapy with Pembrolizumab



Among the 212 randomized patients, 29 had measurable CNS metastases at baseline as assessed by BIRC. Responses in intracranial lesions were observed in 14 of 17 patients treated with RETEVMO and 7 of 12 patients treated with chemotherapy with pembrolizumab.

Overall survival was immature at the time of the PFS interim analysis. At the time of an updated descriptive analysis of OS (43% of prespecified OS events needed for the final analysis), a total of 49 (31%) and 26 (25%) patients died in the RETEVMO and the control arm, respectively. The OS HR was 1.26 (95% CI: 0.78, 2.04). Overall survival may be affected by the imbalance in post-progression therapies. Of 68 control arm patients who had disease progression, 50 patients (74%) received RETEVMO at progression. Of 71 RETEVMO arm patients who had disease progression, 16 (23%) received chemotherapy and/or immune checkpoint inhibitor therapy, and 44 (62%) continued receiving RETEVMO.

14.2 *RET*-Mutant Medullary Thyroid Cancer

LIBRETTO-001

The efficacy of RETEVMO was evaluated in patients with *RET*-mutant MTC enrolled in a multicenter, open-label, multi-cohort clinical trial (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 18.

Table 18: 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 19.

Table 19: Efficacy Results in LIBRETTO-001 (*RET*-Mutant MTC Previously Treated with Cabozantinib or Vandetanib)

	RETEVMO (n = 55)
Overall Response Rate[1] (95% CI)	76% (63%, 87%)
Complete response	18%
Partial response	58%
Duration of Response	
Median in months (95% CI)	45.3 (29.9, NE)
% with ≥12 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 18.

Efficacy results for cabozantinib and vandetanib-naïve *RET*-mutant MTC are summarized in Table 20.

Table 20: Efficacy Results in LIBRETTO-001 (Cabozantinib and Vandetanib-naïve *RET*-Mutant MTC)

	RETEVMO (n = 88)
Overall Response Rate[1] (95% CI)	81% (71%, 88%)
Complete response	28%
Partial response	52%
Duration of Response	
Median in months (95% CI)	NR (51.3, NE)
% with ≥12 months[2]	90%

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NR = not reached, NE = not estimable

LIBRETTO-531

LIBRETTO-531 was a randomized (2:1), multicenter, open-label study (NCT04211337) in adults and adolescents with advance or metastatic *RET*-mutant MTC. The study evaluated the efficacy of RETEVMO versus physicians' choice of cabozantinib or vandetanib in patients with progressive, advanced, kinase inhibitor naïve, *RET*-mutant medullary thyroid cancer.

Patients were randomized to receive either RETEVMO (160 mg twice daily) or physicians' choice of cabozantinib (140 mg once daily) or vandetanib (300 mg once daily). Patients were stratified based on *RET* mutation (M918T vs. other) and intended treatment if randomized to the control arm (cabozantinib vs. vandetanib). The primary outcome was progression-free survival (PFS), as determined by a blinded independent review committee (BIRC) according to RECIST v1.1.

The median age was 55 years (range: 12 to 84), 63% were male, 58% were White, 23% were Asian, 2.4% were Black or African American, and 17% had unknown race. ECOG performance status was 0-1 (98%) or 2 (1.0%) with 0.7% unknown status. 77% of patients had metastatic disease and 6 patients (2.1%) had received 1 prior systemic therapy. *RET* mutation status was detected in 90% of patients using NGS (89% tumor samples; 8% blood or plasma), and 10% using PCR. Of patients enrolled in LIBRETTO-531, 63% had M918T *RET* mutations and 37% had other *RET* mutations.

Efficacy results for LIBRETTO-531 based on the preplanned interim efficacy analysis are provided in Table 21 and Figure 2. At the time of this analysis, overall survival data were immature with 18 deaths observed (14% of pre-specified events).

Table 21: Efficacy Results in LIBRETTO-531: RETEVMO versus Cabozantinib or Vandetanib

	RETEVMO N = 193	**Cabozantinib or Vandetanib N = 98**
PFS		
Number (%) of patients with an event	26 (14%)	33 (34%)
Median in months (95% CI)	NR (NE, NE)	16.8 (12.2, 25.1)
Hazard ratio (95% CI)1	0.280 (95% CI: 0.165, 0.475)	
p-value2	<0.0001	
Overall Response Rate		
ORR (95% CI)	69% (62%, 76%)	39% (29%, 49%)
Complete response	12%	4%
Partial response	58%	35%
Duration of Response		

Median in months (95% CI)	NR (NE, NE)	16.6 (10.4, NE)
Median follow-up time (months)	11.1	12.8

Data from the pre-planned interim efficacy analysis.

[1] Based on the stratified Cox proportional hazard model.

[2] Based on stratified log-rank test.

NR = Not reached; NE = not evaluable

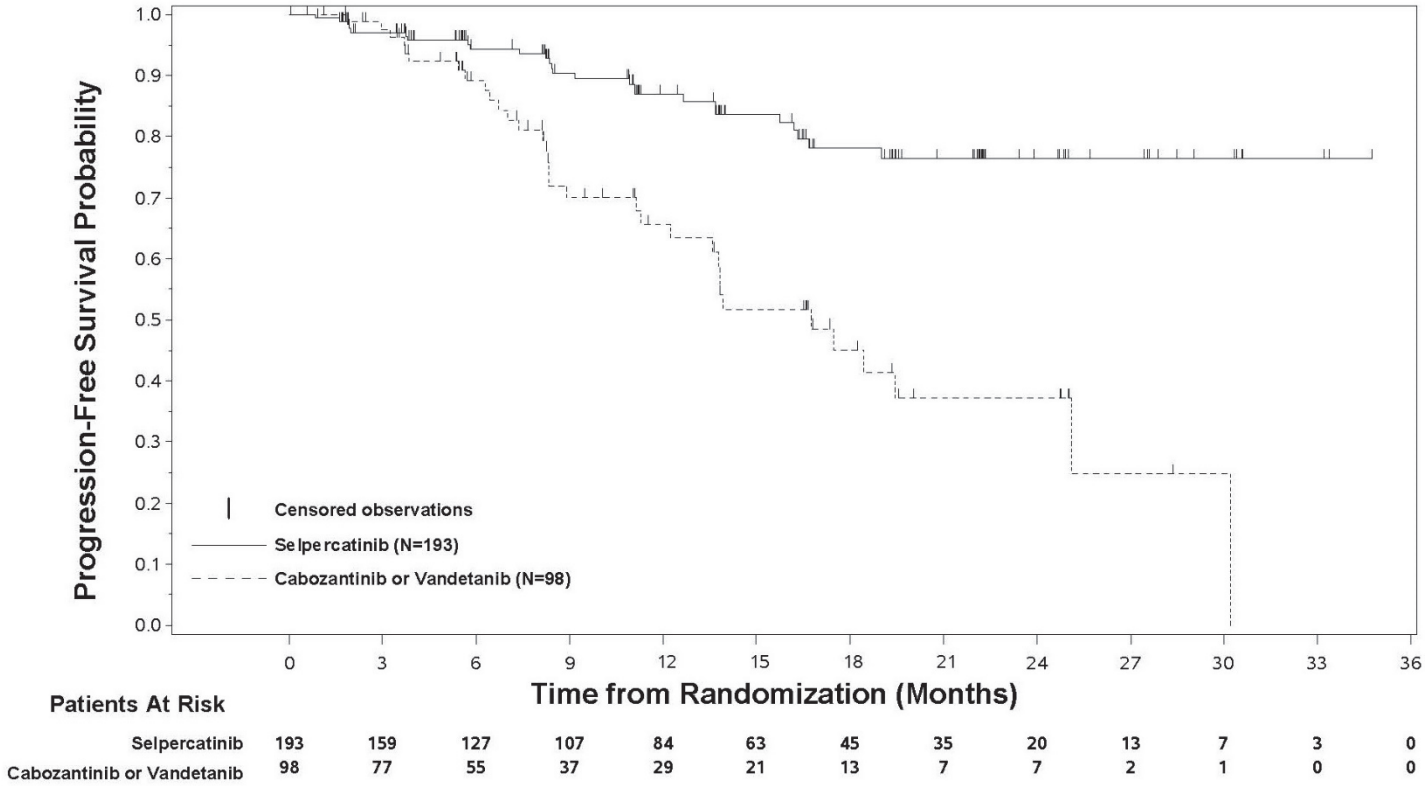


Figure 2: Kaplan-Meier Curves of Progression-Free Survival in LIBRETTO-531: RETEVMO versus Cabozantinib or Vandetanib

Patient-reported overall side effect impact was evaluated weekly in 222 patients (RETEVMO N = 145; cabozantinib or vandetanib N=77) who received at least one dose of treatment by at least 6 months prior to the data cutoff date and responded to the Functional Assessment of Cancer Therapy item GP5 (FACT GP5). Patient-reported overall side effect impact was derived as a proportion of time on treatment with high side effect bother (defined as response of 3 “Quite a bit” or 4 “Very much”) per FACT GP5.

Patient-reported overall side effect impact results for LIBRETTO-531 are provided in Table 22.

Table 22. Descriptive Summary of Patient-reported Overall Side Effect Impact While on Treatment in LIBRETTO-531

	RETEVMO (N=145)	**Cabozantinib or Vandetanib (N=77)**
Mean proportion of time with high side effect bother (95% CI)	8% (4.8%, 10%)	24% (17%, 31%)

% Patients with high side effect bother		
0% of time	61%	30%
≤25% of time	90%	66%

Patient-reported overall side effect impact results were supported by a lower incidence of treatment discontinuation due to adverse reactions for RETEVMO (4.7%) compared to cabozantinib or vandetanib (27%) in patients who received at least one dose of study treatment. The median time on treatment at the data cutoff was 14.5 months in the RETEVMO arm and 8.3 months in the cabozantinib or vandetanib arm in patients who received at least one dose of study treatment.

LIBRETTO-121

The efficacy of RETEVMO was evaluated in pediatric and young adult patients with advanced *RET*-activated solid tumors enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-121**,** NCT03899792)*.* Patients received RETEVMO 92 mg/m^2 orally twice daily until disease progression, unacceptable toxicity, or other reason for treatment discontinuation. Tumor assessments were performed every 8 weeks for one year, then every 12 weeks; responses were assessed according to RECIST 1.1 per BIRC.

Efficacy was evaluated in 14 patients with *RET*-mutant MTC who were non-responsive to available therapies or had no standard systemic curative therapy available. The median age was 14 years (range 2 to 20); 64% were male; 71% were White, 14% were Black or African American; and 14% were Hispanic/Latino. Patients had metastatic (71%) or locally advanced (29%) disease; 43% had measurable disease at baseline; 21% had received prior systemic therapy. *RET*-mutant status was detected in 79% of patients using NGS tumor samples and in 21% using PCR.

Efficacy results for *RET*-mutant MTC in pediatric and young adult patients are summarized in Table 23.

Table 23: Efficacy Results in LIBRETTO-121 (*RET*-Mutant MTC)

	RETEVMO (n = 14)
Overall Response Rate[1] (95% CI)	43% (18, 71)
Complete response	7%
Partial response	36%
Duration of Response	
Median in months (95% CI)	NR (NE, NE)
% with ≥12 months[2]	100%
% with ≥18 months[2]	67%

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NR = not reached; NE = not estimable

14.3 *RET* Fusion-Positive Thyroid Cancer

LIBRETTO-001

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 65 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 who were previously treated, in separate cohorts.

The median age was 59 years (range 20 to 88); 49% were male; 65% were White, 20% were Asian, 4.6% were Black or African American; and 11% were Hispanic/Latino. ECOG performance status was 0-1 (94%) or 2 (6%). All (100%) patients had metastatic disease with primary tumor histologies including papillary thyroid cancer (83%), poorly differentiated thyroid cancer (9%), anaplastic thyroid cancer (6%) and Hurthle cell thyroid cancer (1.5%). Previously treated patients had received a median of 1 prior therapy (range 1–4). *RET* fusion-positive status was detected in 97% of patients using NGS (89% tumor samples; 8% blood or plasma samples), and 3% using other local testing methods.

Efficacy results for *RET* fusion-positive thyroid cancer are summarized in Table 24.

Table 24: Efficacy Results in LIBRETTO-001 (*RET* Fusion-Positive Thyroid Cancer)

	RETEVMO Previously Treated (n = 41)	**RETEVMO Systemic Therapy Naïve (n = 24)**
Overall Response Rate[1] (95% CI)	85% (71%, 94%)	96% (79%, 100%)
Complete response	12%	21%
Partial response	73%	75%
Duration of Response		
Median in months (95% CI)	26.7 (12.1, NE)	NE (42.8, NE)
% with ≥12 months[2]	54	65

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NE = not estimable

Responses were observed in patients with each histology represented, including 3 of 4 patients with anaplastic thyroid cancer (all partial responses) and 6 of 6 patients with poorly differentiated thyroid cancer (1 complete response, 5 partial responses).

LIBRETTO-121

The efficacy of RETEVMO was evaluated in pediatric and young adult patients with advanced *RET*-activated solid tumors enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-121**,** NCT03899792) *[see Clinical Studies (14.2)].*

Efficacy was evaluated in 10 patients with *RET* fusion-positive thyroid cancer who were non-responsive to available therapies or had no standard systemic curative therapy available. The median age was 13.5 years (range 12 to 20); 60% were male; 40% were White, 50% were Asian; and 30% were Hispanic/Latino. All (100%) patients had metastatic disease and papillary thyroid cancer histology; 40% had measurable disease at baseline; 30% had received prior systemic therapy. *RET* fusion-positive status was detected in 90% of patients using NGS tumor samples and in 10% using FISH. Efficacy results for *RET* fusion-positive thyroid cancer in pediatric and young adult patients are summarized in Table 25.

Table 25: Efficacy Results in LIBRETTO-121 (*RET* Fusion-Positive Thyroid Cancer)

	RETEVMO (n = 10)
Overall Response Rate[1] (95% CI)	60% (26, 88)
Complete response	30%
Partial response	30%
Duration of Response	
Median in months (95% CI)	NR (NE, NE)
% with ≥12 months[2]	83%
% with ≥18 months[2]	50%

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NR = not reached; NE = not estimable

14.4 Other *RET* Fusion-Positive Solid Tumors

LIBRETTO-001

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; and 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 26 and Table 27.

Table 26: 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 27: 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.

LIBRETTO-121

The efficacy of RETEVMO was evaluated in pediatric and young adult patients with advanced *RET*-activated solid tumors enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-121**,** NCT03899792) *[see Clinical Studies (14.2)].*

Efficacy was evaluated in one patient with locally advanced refractory *RET*-fusion positive malignant peripheral nerve sheath tumor who did not respond. Responses were observed in patients with *RET* fusion-positive thyroid cancer *[see Clinical Studies (14.3)].*

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

RETEVMO capsules are supplied as follows:

Capsule Strength	Description	Package Configuration	NDC Number
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

RETEVMO tablets are supplied in bottles with desiccant in the following configurations:

Tablet Strength	Description	Package Configuration	NDC Number
40 mg	Light gray, film coated, round tablets debossed with “Ret 40” on one side and “5340” on the other side	60 count bottle	NDC 0002-5340-60
80 mg	Dark red-purple, film coated, round tablets debossed with “Ret 80” on one side and ”6082” on the other side	60 count bottle	NDC 0002-6082-60
120 mg	Light purple, film coated, round tablets debossed with “Ret 120” on one side and “6120” on the other side	60 count bottle	NDC 0002-6120-60
160 mg	Light pink, film coated, round tablets debossed with Ret “160” on one side and “5562” on the other side	60 count bottle	NDC 0002-5562-60

Storage and Handling

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)]*.

Slipped Capital Femoral Epiphysis/Slipped Upper Femoral Epiphysis

Advise pediatric patients and caregivers to contact their healthcare provider promptly to report any signs and symptoms indicative of slipped capital femoral epiphysis/slipped upper femoral epiphysis *[see Warnings and Precautions (5.11)]*.

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

D0.08-RET-0006-USPI-20240927

PATIENT INFORMATION

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

RETEVMO® (reh-TEHV-moh)
(selpercatinib)
tablets

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 2 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 2 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 and children 2 years of age and older 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 2 years of age for the treatment of:
  - advanced MTC or MTC that has spread who require a medicine by mouth or injection.
  - advanced thyroid cancer or thyroid cancer that has spread who require a medicine by mouth or injection, and have received radioactive iodine and it did not work or is no longer working.
  - locally advanced solid tumors or solid tumors that have spread, and have gotten worse on or after other treatment or there are no satisfactory treatment options.
- in children for other conditions.

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.

During treatment with RETEVMO, you should avoid taking:

- St. John's wort
- proton pump inhibitors (PPIs), such as dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole sodium, and rabeprazole
- H2 blockers, such as famotidine, nizatidine, and cimetidine
- antacids that contain aluminum, magnesium, calcium, simethicone, or buffered medicines

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.
- Swallow RETEVMO capsules and tablets whole. Do not crush or chew.
- Do not give RETEVMO capsule to your child if they are unable to swallow a capsule.
- 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 H2 blocker (such as famotidine, nizatidine, and cimetidine), take RETEVMO 2 hours before or 10 hours after taking the H2 blocker.
- 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 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) can happen during treatment 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
- **Hip joint problems (slipped capital femoral epiphysis or slipped upper femoral epiphysis) in children.** Tell your healthcare provider right away if you develop signs and symptoms of hip problems, including hip or knee pain or a painless limp.

The most common side effects of RETEVMO in adults with solid tumors include:

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

The most common side effects of RETEVMO in children 2 years and older with solid tumors include:

- muscle and bone pain
- diarrhea
- headache
- nausea
- vomiting
- coronavirus infection
- stomach-area (abdominal) pain
- tiredness
- fever
- bleeding

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

The most common severe abnormal laboratory test results with RETEVMO in children 2 years and older with solid tumors include decreased levels of calcium in the blood, decreased red blood cell count, and decreased white blood cell count.

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 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
Capsules: colloidal silicon dioxide and microcrystalline cellulose. 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.

Tablets: croscarmellose sodium, hydroxypropyl cellulose, mannitol, microcrystalline cellulose, and sodium stearyl fumarate. The tablet film coating material contains polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc.

Additionally, the film coating of the 40 mg, 80 mg, and 120 mg tablets contains ferrosoferric oxide and the film coating of the 80 mg, 120 mg, and 160 mg tablets contain ferric oxide.

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

C0.04-RET-0006-PPI-20240927

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 09/2024

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213246Orig1s011

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
Application Number(s)	213246 S11, 218160 S3
Priority or Standard	Standard
Submit Date(s)	November 29, 2023
Received Date(s)	November 29, 2023
PDUFA Goal Date	September 29, 2023
Division/Office	Division of Oncology 2 / Office of Oncologic Drugs
Review Completion Date	*Electronic stamp date*
Established Name	selpercatinib
(Proposed) 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 Tablets: 40 mg, 80 mg, 120 mg, 160 mg
Dosing Regimen	Adult and adolescent patients 12 years of age or older, the recommended dosage is based on weight: • Less than 50 kg: 120 mg orally twice daily • 50 kg or greater: 160 mg orally twice daily Pediatric patients 2 to less than 12 years of age, the recommended dosage is based on body surface area: • 0.33 to 0.65 m2: 40 mg orally three times daily • 0.66 to 1.08 m2: 80 mg orally twice daily • 1.09 to 1.52 m2: 120 mg orally twice daily • ≥1.53 m2: 160 mg orally twice daily

Applicant Proposed Indication(s)/Population(s)	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
Recommendation on Regulatory Action	Traditional Approval
Recommended Indication(s)/Population(s) (if applicable)	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

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Tselaine Jones Smith
Pharmacology/Toxicology Reviewer(s)	N/A
Pharmacology/Toxicology Team Leader(s)	N/A
Office of Clinical Pharmacology Reviewer(s)	Miao Zhao
Office of Clinical Pharmacology Team Leader(s)	Jeanne Fourie Zirkelbach
Clinical Reviewer	Elizabeth Duke
Clinical Team Leader	Diana Bradford
Statistical Reviewer	Arup Sinha
Statistical Team Leader	Xiaoxue Li
Associate Director for Labeling (ADL)	Barbara Scepura
Cross-Disciplinary Team Leader	Diana Bradford
Deputy Division Director (OCP)	Stacy Shord
Deputy Division Director (OB)	Pallavi Mishra-Kalyani
Deputy Division Director (OOD)	Nicole Drezner
Office Director (or designated signatory authority)	N/A

Additional Reviewers of Application

OPQ	Qi Liu, Roshni Ramchandani
OPDP	Mispa Ajua-Alemanji, Rachel Conklin
OSI	N/A
OSE/DEPI	N/A
OSE/DMEPA	Janine Stewart Ashleigh Lowery
OSE/DRISK	N/A
Other	N/A

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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
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine transaminase
AST	aspartate transaminase
BICR	Blinded Independent Central Review
BID	twice daily
BLA	biologics license application
CI	confidence interval
CIR	cumulative incidence rate
CNS	central nervous system
COA	clinical outcome assessment
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Event
C_{trough}	trough concentration
CV	coefficient of variation
DOR	duration of response
EA	East Asian
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	estimated glomerular filtration rate
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 version 3.0
ER	exposure-response

FDA	United States Food and Drug Administration
GCP	good clinical practice
HR	heart rate
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
MTC	medullary thyroid cancer
NDA	new drug application
NE	not evaluable
NGS	next-generation sequencing
NME	new molecular entity
No.	number
NSCLC	non-small cell lung cancer
ODxTT	Oncomine Dx Target Test
ORR	objective response rate
OS	overall survival
OSI	Office of Scientific Investigation
PD-L1	programmed death-ligand 1
PFS	progression free survival
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPK	population PK
PRO	patient reported outcome
PT	preferred term
Q3W	every 3 weeks
QTc	corrected QT interval
QTcF	Fredericia's corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumours
RET	REarranged during Transfection

SAE	serious adverse event
SAP	statistical analysis plan
sNDA	supplemental new drug application
TC	thyroid cancer
TTCD	time to confirmed deterioration
TEAE	treatment emergent adverse event
USPI	United States Package Insert

1 Executive Summary

1.1. 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, including non-small cell lung cancer.

On May 8, 2020, selpercatinib was granted accelerated approval 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.

On September 21, 2022, the selpercatinib indication for NSCLC was granted traditional approval. In addition, the Oncomine™ Dx Target Test was approved expanding the indications for use to include a companion diagnostic indication for the detection of *RET* fusions in NSCLC patients who may benefit from selpercatinib.

Selpercatinib is also approved for:

- Adult and pediatric patients 2 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 2 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)
- Adult and pediatric patients 2 years of age and older 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[1]

[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).

The recommended selpercatinib dosage is as follows:

- Adult and adolescent patients 12 years of age or older, the recommended dosage is based on weight:
  - Less than 50 kg: 120 mg orally twice daily
  - 50 kg or greater: 160 mg orally twice daily
- Pediatric patients 2 to less than 12 years of age, the recommended dosage is based on body surface area:

- 0.33 to 0.65 m2: 40 mg orally three times daily
- 0.66 to 1.08 m2: 80 mg orally twice daily
- 1.09 to 1.52 m2: 120 mg orally twice daily
- ≥1.53 m2: 160 mg orally twice daily

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant previously provided substantial evidence of effectiveness of selpercatinib 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, as described in the multidisciplinary review dated September 21, 2022 (sNDA 213246 Supplement 7). The traditional approval was based on objective response rate (ORR) and duration of response (DOR) data, with substantial durability of responses in additional patients supported by consistent ORR results, in both treatment-naïve and previously treated patients with *RET* fusion-positive NSCLC enrolled in Study LOXO-RET-17001 (LIBRETTO-001), an international, single-arm, dose-escalation and multi-cohort expansion study that supported the accelerated approval of selpercatinib. FDA did not require a randomized controlled trial to verify the benefit of selpercatinib for this indication due to the perceived lack of equipoise with high overall response rates with prolonged durations of response in a rare biomarker driven population. However, a randomized trial was conducted by the Applicant and submitted to FDA in this supplemental application to update product labeling with these new efficacy results for the existing indication.

This supplement (sNDA 213246 Supplement 11) provides important information about the effectiveness of selpercatinib not furnished by the studies that provided primary support for its approval for *RET* fusion-positive NSCLC. Specifically, the results of Study LIBRETTO-431, a multi-regional, open-label, randomized, active-controlled trial of selpercatinib versus platinum-based and pemetrexed chemotherapy with or without pembrolizumab in patients with treatment-naïve *RET* fusion-positive, unresectable locally advanced or metastatic NSCLC, provide information about the nature and size of the treatment effect of selpercatinib in patients with *RET* fusion-positive NSCLC, as well as randomized safety data which complement the existing safety database from single arm trials.

The primary efficacy population included 212 patients enrolled in LIBRETTO-431 with an intent to treat with pembrolizumab if randomized to the control arm (129 into selpercatinib arm and 83 into chemotherapy with pembrolizumab arm). A 13.6-month median improvement in progression-free survival (PFS) as determined by a blinded independent review committee (BIRC) according to RECIST v1.1, the major efficacy outcome measure, was observed at the first planned interim analysis (median PFS: 24.8 months in selpercatinib arm vs. 11.2 months in control arm), with a hazard ratio (HR) of 0.47 (95% Confidence Interval [CI] 0.31, 0.70). Additionally, an improvement in ORR was observed in the selpercatinib arm compared to the chemotherapy with pembrolizumab arm (84% [95% CI 76, 90]) vs. 65% [95% CI 54, 75]).

Overall survival (OS) was immature at the time of the PFS interim analysis. At the time of an updated descriptive analysis of OS (43% of prespecified OS events needed for the final analysis), a total of 49 (31%) and 26 (25%) patients died in the selpercatinib and the control arm, respectively. The OS HR was 1.26 (95% CI: 0.78, 2.04). Overall survival may be affected by the imbalance in post-progression therapies. Of 68 patients on the control arm who had disease progression, 50 patients (74%) received selpercatinib at progression. Of 71 patients on the selpercatinib arm who had disease progression, 16 (23%) received chemotherapy and/or immune checkpoint inhibitor therapy, and 44 (62%) continued receiving selpercatinib.

The review team considered that the benefits of selpercatinib outweighed the risks in the intended population even though the point estimate of the OS HR was greater than 1.0 based on the factors described herein:

- The prior determination of substantial evidence of effectiveness based on a high ORR (>80% in two adequate and well-controlled trials) with substantial durability (>20 months in two adequate and well-controlled trials).
- A >1 year median improvement in PFS compared to chemo-immunotherapy in LIBRETTO-431 with a HR of 0.47 (95% CI: 0.31, 0.70).
- The reduced burden to patients for an oral therapy option compared to combination intravenous (IV) therapies.
- The study design of LIBRETTO-431 impacted the interpretability of the overall survival results, primarily in that crossover was permitted and the majority of patients on the control arm went on to receive selpercatinib in the crossover phase of the study or alternatively, a commercially available RET inhibitor off study. In addition, most patients in the selpercatinib arm did not receive standard of care chemo-immunotherapy at any point during their treatment course. Therefore, it is possible that treatment with only one effective therapy (i.e., selpercatinib) as opposed to two effective therapies (i.e., selpercatinib plus chemo-immunotherapy) may impact overall survival. However, the study was not designed to evaluate this question and the data are immature; therefore, it is challenging to draw definitive conclusions regarding this issue based on the available data. A post-marketing commitment (PMC) will be issued for provision of the final OS results for LIBRETTO-431.
- While the safety profiles of selpercatinib vs. chemo-immunotherapy differed, there was no clear evidence that worse toxicity would result in differential overall survival for patients receiving selpercatinib. A higher number of patient deaths were observed on the selpercatinib arm; however, the events were not clearly due to selpercatinib-related toxicity.
- Although there were higher incidences of adverse events (AEs) leading to treatment discontinuation, Grade ≥ 3 AEs, and serious AEs observed in patients receiving selpercatinib compared to chemo-immunotherapy, patients who received standard of care chemotherapy with or without immunotherapy had a shorter median time on treatment with a fixed number of treatment cycles, whereas patients who received selpercatinib continued on treatment indefinitely until progressive disease or unacceptable toxicity.

This imbalance in treatment length may have contributed to a higher incidence and greater severity of some AEs observed in patients on the selpercatinib arm.

- The safety profile of selpercatinib in patients with *RET* fusion positive NSCLC is further supported by that observed in LIBRETTO-531, a randomized study of selpercatinib compared to physician's choice of cabozantinib or vandetanib in patients with medullary thyroid cancer with a *RET* mutation. Although OS data were immature at the time of the interim PFS analysis supporting traditional approval (see FDA review for sNDA 213246-S013), neither an OS detriment nor an increased rate of fatal events related to selpercatinib were observed.

Therefore, the review team concludes that use of selpercatinib for the initial treatment of *RET* fusion positive NSCLC should remain an option for patients based on superior tumor control, higher objective response rate and an alternative oral mode of administration when compared to combination chemo or chemo-immunotherapy. The team recommends inclusion of the results of Study LIBRETTO-431 in the product labeling for selpercatinib as this study provides important information about the safety and effectiveness of selpercatinib not furnished by the studies that provided primary support for effectiveness. A more mature overall survival analysis of LIBRETTO-431 will be requested as a post-marketing commitment.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Lung cancer is the leading cause of cancer deaths, making up 20% of all cancer deaths in 2024 (Siegel et al, 2024). Despite recent advances in the field, the prognosis for patients with metastatic non-small cell lung cancer (NSCLC) remains poor, with a 5-year relative survival rate of less than 10% (American Cancer Society, 2024).

RET gene fusions are rare oncogenic alterations observed in 1-3% of patients with NSCLC, and these alterations are typically mutually exclusive of other known validated oncogenic drivers (Ferrara et al, 2018). First-line treatment options for these patients includes a targeted RET inhibitor (selpercatinib or pralsetinib); other recommended options include chemotherapy with or without immunotherapy (NCCN Guidelines, v8.2024). The role of immunotherapy in patients with *RET*-altered NSCLC is debated.

Selpercatinib is an oral inhibitor of the RET receptor tyrosine kinase which was granted accelerated approval in May 2020 for the treatment of adult patients with metastatic *RET* fusion-positive NSCLC based on an overall response rate (ORR) of 85% (95% CI 70, 94) in 39 treatment-naïve patients and of 64% (95% CI 54, 73) in 105 patients previously treated with platinum chemotherapy. Traditional approval for this indication was granted in September 2021 based on substantial durability of responses in additional patients supported by consistent ORR results in Study LIBRETTO-001, the same international, single-arm, dose-escalation and multi-cohort expansion study that supported the accelerated approval of selpercatinib.

The current supplement (S11) provides important information about the effectiveness of selpercatinib not furnished by the studies that provided primary support for effectiveness, as it provides additional information about the nature and size of the treatment effect of selpercatinib in patients with treatment-naïve *RET* fusion-positive NSCLC, as well as randomized safety data which complement the existing safety database from single arm trials.

Study LIBRETTO-431 was a multi-regional, open-label, randomized, active-controlled trial of selpercatinib versus platinum-based and pemetrexed chemotherapy with or without pembrolizumab in patients with treatment-naïve *RET* fusion-positive, unresectable locally advanced or metastatic NSCLC. The primary efficacy population included 212 patients enrolled with an intent to treat with pembrolizumab if randomized to the control arm (129 into selpercatinib arm and 83 into chemotherapy with pembrolizumab arm). A 13.6-month improvement in PFS as determined by BIRC according to RECIST v1.1, the major efficacy outcome measure, was observed at the first planned interim analysis (median PFS: 24.8 months in selpercatinib arm vs. 11.2 months in control arm), with HR 0.47 (95% CI: 0.31, 0.70). OS was immature at the time of the PFS interim analysis. At the time of an updated descriptive analysis of OS (43% of prespecified OS events needed for the final analysis), a total

of 49 (31%) and 26 (25%) patients died in the selpercatinib and the control arm, respectively. The OS HR was 1.26 (95% CI: 0.78, 2.04). While the point estimate of the OS HR was greater than 1.0, the study design of LIBRETTO-431 impacted the interpretability of the OS results. Considerations include the immaturity of OS data, the high rate of crossover, the commercial availability of RET inhibitors off study, the continued use of selpercatinib post-progression in the experimental arm and the limited use of standard chemo-immunotherapy as a post-progression therapy in the experimental arm. While there were numerically more high-grade adverse events and dosage modifications on the selpercatinib arm, the median time on treatment was double that of the control arm, and there did not appear to be a clear safety signal that would result in worse overall survival for patients receiving selpercatinib. A post-marketing commitment will be included in the approval letter to obtain final OS results from LIBRETTO-431.

The review team concluded that the benefits of selpercatinib for the treatment of adult patients with locally advanced or metastatic *RET* fusion-positive NSCLC outweigh the risks and recommend including the results of Study LIBRETTO-431 in the product labeling for selpercatinib as this study provides important information about the effectiveness of selpercatinib not furnished by the studies that provided primary support for effectiveness.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Lung cancer is the leading cause of cancer deaths, making up 20% of all cancer deaths in 2024 (Siegel et al, 2024). Non-small cell lung cancer (NSCLC) accounts for 80-85% of lung cancer patients and adenocarcinoma is the most common histological subtype. In the US, the 5-year relative survival rate for patients with NSCLC with distant disease is 9% (American Cancer Society, 2024). • The incidence of *RET* gene fusions in metastatic NSCLC is 1-3% and these alterations are typically mutually exclusive of other known validated oncogenic drivers (Ferrara et al, 2018).	Locally advanced or metastatic *RET* fusion-positive NSCLC is a life-threatening condition with poor survival.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Selpercatinib and pralsetinib are targeted therapies approved for the treatment of adults with advanced or metastatic *RET* fusion-positive NSCLC. • Other systemic therapies (such as chemotherapy with or without immunotherapy) are categorized as "other recommended" first-line treatment options for *RET*-positive advanced or metastatic NSCLC per NCCN guidelines; these are also recommended as subsequent therapy options in patients whose disease progressed after initial treatment (NCCN Guidelines, v8.2024).	Selpercatinib is an approved first-line treatment for this population and is recommended for use by NCCN Guidelines.
Benefit	• Substantial evidence of effectiveness of selpercatinib for the intended population was previously established, as described in the multidisciplinary review dated September 21, 2022 (sNDA 213246 Supplement 7). The current supplement (S11) provides important information about the effectiveness of selpercatinib not furnished by the studies that provided primary support for effectiveness. • Study LIBRETTO-431 was a multi-regional, open-label, randomized, active-controlled trial of selpercatinib versus platinum-based and pemetrexed chemotherapy with or without pembrolizumab in patients with treatment-naïve *RET* fusion-positive, unresectable locally advanced or metastatic NSCLC. • The primary efficacy population included 212 patients enrolled with an intent to treat with pembrolizumab if randomized to the control arm (129 into selpercatinib arm and 83 into chemotherapy with pembrolizumab arm). A 13.6-month improvement in PFS as determined by BIRC according to RECIST v1.1, the major efficacy	While selpercatinib was previously approved for the proposed indication, this supplemental NDA provides additional information about the nature and size of the treatment effect of selpercatinib in patients with treatment-naïve *RET* fusion-positive NSCLC, as well as randomized safety data which complement the existing safety database from single arm trials. The 13.6-month improvement in PFS with selpercatinib compared to chemo-immunotherapy provides evidence of a clinically meaningful benefit of selpercatinib in this population. While the point estimate of the OS HR was greater than 1.0, the study design of LIBRETTO-431 impacted the interpretability

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	outcome measure, was observed at the first planned interim analysis (median PFS: 24.8 months in selpercatinib arm vs. 11.2 months in control arm), with HR 0.47 (95% CI: 0.31, 0.70). • OS was immature at the time of the PFS interim analysis. At the time of an updated descriptive analysis of OS (43% of prespecified OS events needed for the final analysis), a total of 49 (31%) and 26 (25%) patients died in the selpercatinib and the control arm, respectively. The OS HR was 1.26 (95% CI: 0.78, 2.04). OS may be affected by the imbalance in post-progression therapies.	of the OS results. Considerations include the immaturity of OS data, the high rate of crossover, the commercial availability of RET inhibitors off study, the continued use of selpercatinib post-progression in the experimental arm and the limited use of standard chemo-immunotherapy as a post-progression therapy in the experimental arm. A post-marketing commitment will be included in the approval letter to obtain final OS results from LIBRETTO-431.
Risk and Risk Management	• The primary safety population in LIBRETTO-431 included 158 patients with unresectable locally advanced or metastatic *RET* fusion-positive NSCLC. • The most common (≥25%) treatment-emergent adverse events (TEAEs) were hypertension, diarrhea, edema, dry mouth, rash, fatigue, abdominal pain, and musculoskeletal pain. • The most common (≥5%) Grade 3 or 4 laboratory abnormalities were increased ALT, increased AST, and decreased lymphocytes. • While there were numerically more high-grade adverse events and dosage modifications on the selpercatinib arm, the median time on treatment was double that of the control arm, and there did not appear to be a clear safety signal that would result in worse overall survival for patients receiving selpercatinib.	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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The understanding of the safety of selpercatinib is supported by a broader population of 796 patients with *RET* fusion-positive advanced solid tumors who received selpercatinib in single-arm study LIBRETTO-001.	

1.4. Patient Experience Data

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

					Section where discussed, if applicable
X	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as			
		X	Patient reported outcome (PRO)		Section 8.1.2
		□	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			

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 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 _____

Diana Bradford, MD
Cross-Disciplinary Team Leader

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2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

RET gene fusions lead to increased oncogenic signalling and are present in approximately 1% of patients with NSCLC of both Asian and European descent (Kohno et al. 2013; Ferrara et al. 2018). *RET* fusion-positive lung cancer has been associated with poor prognostic features including early lymph node metastases and poor differentiation (Wang et al. 2012; Liu et al. 2019). Patients with *RET* fusion-positive lung cancer have brain metastases at rates similar to the overall NSCLC population, in approximately 20% to 50% of patients (Fenske et al. 2017; Drilon et al. 2018). It is also associated with identifiable clinicopathologic characteristics, including younger age, female sex, never-smoker status, early lymph node metastases, poor differentiation, and a solid-predominant subtype (Wang et al. 2012). *RET* fusions are generally mutually exclusive with other driver alterations such as *EGFR*, *ROS1*, *ALK* (Farago and Azzoli 2017).

The FDA's Assessment:

Lung cancer is the leading cause of cancer deaths, making up 20% of all cancer deaths in 2024 (Siegel et al, 2024). Non-small cell lung cancer (NSCLC) accounts for 80-85% of lung cancer patients and adenocarcinoma is the most common histological subtype. In the US, the 5-year relative survival rate for patients with NSCLC with distant disease is 9% (American Cancer Society, 2024).

Genetic alterations in the RET protooncogene have been implicated in the pathogenesis of several human cancers. The incidence of *RET* gene fusions in metastatic NSCLC is 1-3% and these alterations are typically mutually exclusive of other known validated oncogenic drivers (Ferrara et al, 2018). The most common *RET* fusions in NSCLC are KIF5B-RET (70-90%) and CCDC6-RET (10-25%). *RET* fusions in NSCLC are associated with younger age (≤ 60 years of age), female sex, adenocarcinoma histology, and minimal or no prior tobacco exposure. (Drilon et al, 2018; Li et al, 2019). The frequency of brain metastases at the time of diagnosis in patients with advanced *RET*-rearranged NSCLC is approximately 25% with a lifetime prevalence of brain metastases of 46% (Drilon et al, 2018).

2.2. Analysis of Current Treatment Options

The Applicant's Position:

The selective *RET* inhibitors selpercatinib and pralsetinib (GAVRETO, Blueprint Medicines Corporation) are both approved by the FDA for the treatment of patients with *RET* fusion-positive

NSCLC. The NCCN guidelines recommend selective *RET* inhibitors (selpercatinib or pralsetinib) as the preferred front-line therapy for patients with advanced or metastatic *RET* fusion-positive NSCLC (NCCN 2023), over platinum-based regimens with or without immunotherapy, which are a standard of care for patients without driver alterations. However, despite this guidance, platinum-based chemotherapy with immunotherapy is still commonly used. The platinum, pemetrexed and pembrolizumab combination has been one of the most frequently used of these regimens based on the results initially reported in 2018 in the KEYNOTE-189 study (Gandhi et al. 2018). The 5-year outcomes from the Phase 3 KEYNOTE-189 study were recently published (Garassino et al. 2023). The modified PFS and modified OS for patients treated with pembrolizumab plus pemetrexed-platinum was 9.0 months (95% CI: 8.1–10.4 months) and 22.0 months (95% CI: 19.5–24.5 months), respectively.

The drivers for the continued use of platinum-based chemotherapy and pembrolizumab over selective *RET* inhibitors in patients with *RET* fusion-positive NSCLC are multi-factorial and includes the lack of randomized data comparing these regimens and the reluctance to test for rare alterations like *RET*. Despite the international consensus guidelines recommending molecular profiling of tumors as part of routine evaluation in patients with NSCLC (Lindeman et al. 2018; Planchard et al. 2020; NCCN 2023) and the availability of the FDA-approved companion diagnostic for selpercatinib (ODxTT), testing of newly diagnosed patients for *RET* fusions is either not always performed or often done sequentially after negative results for the most common genomic tumor aberrations in NSCLC (for example, *EGFR*, and *ALK*). This approach may lead to targeted treatment delays or having patients start non-targeted therapies such as chemotherapy with or without immunotherapy, or both (Robert et al. 2022).

The results of LIBRETTO-431 provide comparative data to define the optimal treatment regimen for patients with newly diagnosed advanced *RET* fusion-positive NSCLC and also reinforce the importance of timely and comprehensive genomic testing for initial treatment decisions.

The FDA's Assessment:

FDA agrees with the Applicant's summary of available front-line therapy for patients with advanced or metastatic *RET* fusion-positive NSCLC. Selpercatinib and pralsetinib are targeted therapies approved for the treatment of adults with advanced or metastatic *RET* fusion-positive NSCLC. The NCCN guidelines state that other systemic therapies (such as chemotherapy with or without immunotherapy) are categorized as "other recommended" first-line treatment options for *RET*-positive advanced or metastatic NSCLC; these are also recommended as subsequent therapy options in patients whose disease progressed after treatment with selpercatinib, pralsetinib, or cabozantinib (NCCN Guidelines, v8.2024). While there have been some small studies suggesting variable efficacy of immunotherapy in patients with RET-altered tumors, this finding has not been definitively established (Mazieres et al, 2019; Calles et al, 2020).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

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

Table 3.1. Summary of Regulatory Interactions

Date	Activity/Information
30 August 2018	Breakthrough Therapy designation for "*the treatment of patients with metastatic RET fusion-positive non-small cell lung cancer who require systemic therapy and have progressed following platinum-based chemotherapy and an anti-PD-1 or anti-PD-L1 therapy*"
17 July 2019	IND application 144697. The submission package included protocol for LIBRETTO-431 study
13 August 2019	Notification of full clinical hold from FDA during teleconference
14 September 2019	Full Clinical Hold Letter. Main FDA concerns: • The protocol contained no information regarding potential retrospective central testing for confirmation of *RET* status. • There was no evidence that selpercatinib had anti-tumor activity in *RET* wild-type NSCLC, the observed treatment effects in patients who were enrolled based on false positive results would not provide accurate information regarding the treatment effects of selpercatinib in the intended population. • Patients who were enrolled based on false positive results and randomly assigned to the experimental arm would receive an ineffective drug
30 September 2019	Complete Response to Clinical Hold containing: • plan for a companion diagnostic development • rationale for using local testing to identify *RET* gene fusions • proposal that patients were to be enrolled based on either a locally available NGS panel assay performed in a CLIA-certified (US sites) or an accredited (outside of the US) laboratory. PCR or other multiplex testing performed in an accredited laboratory, according to relevant national guidelines, would be also considered outside of the US, and • proposal for retrospective central testing.
04 October 2019	Lilly received additional comments and information requests from FDA related to statistical methods not related to clinical hold
23 October 2019	Teleconference held between Lilly, Loxo, and FDA where an agreement was reached on mitigation actions to address FDA's concerns
25 October 2019	Teleconference summary submitted to IND
30 October 2019	Clinical Hold Letter was removed
30 October 2019	Orphan Drug designation for "*the treatment of RET fusion-positive NSCLC*"

Date	Activity/Information
04 December 2019	Initial NDA 213246 submitted
08 May 2020	Accelerated approval granted for *RET* fusion-positive NSCLC and TC, and *RET*-mutant MTC based on LIBRETTO-001 data, and PMR was agreed for the confirmatory evidence. For the NSCLC indication, it did not include a randomized, active control study, and was based on LIBRETTO-001 as a confirmatory trial. (b) (4) (b) (4) (b) (4)
23 November 2021	Efficacy Supplement 007 submitted to NDA 213246 to fulfill accelerated approval requirement related to the *RET* fusion-positive NSCLC indication
21 September 2022	Regular approval granted 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*"

Abbreviations: CLIA = Clinical Laboratory Improvement Amendment; IND = investigational new drug; Lilly = Eli Lilly and Company; MTC = medullary thyroid cancer; NDA = new drug application; NGS = next-generation sequencing; NSCLC = non-small cell lung cancer; PCR = polymerase chain reaction; PD-1 = programmed death-1; PD-L1 = programmed death ligand-1; PMR = postmarketing requirement; *RET* = REarranged during Transfection; TC = thyroid cancer.

The FDA's Assessment:

FDA agrees with the Applicant's position. Notably, in September 2022, FDA granted traditional approval to selpercatinib 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. FDA did not require a randomized controlled trial to verify the clinical benefit of selpercatinib for this indication due to the perceived lack of equipoise with high overall response rates with prolonged durations of response in a rare biomarker driven population. However, the LIBRETTO-431 trial was conducted and submitted to FDA in this supplemental application with a request to update product labeling with new efficacy results for the same existing indication.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

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

Table 3.2. Selpercatinib: Key Regulatory Interactions in the U.S.

Date	Activity/Information
21 August 2023	A pre-sNDA meeting held between Lilly and FDA to discuss LIBRETTO-431 topline results

Abbreviations: Lilly = Eli Lilly and Company; sNDA = supplemental new drug application.

The FDA's Assessment:

FDA agrees with the Applicant's position.

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

4.1. 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.

4.2. Product Quality

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

4.3. Clinical Microbiology

No clinical microbiology data were submitted in the supplemental application.

4.4. Devices and Companion Diagnostic Issues

No device or companion diagnostic data were submitted in the supplemental application. Companion diagnostics for *RET* alterations were previously approved as follows:

Diagnostic Name (Manufacturer)	**Indication - Sample Type**	**Biomarker(s) (Details)**	**PMA / 510(k) / 513(f)(2) / HDE (Approval / Clearance / Grant Date)**
FoundationOne CDx (Foundation Medicine, Inc.)	Solid Tumors - Tissue	*RET* fusions	P170019/S043 (10/06/2023)
Oncomine Dx Target Test (Life Technologies Corporation)	Medullary Thyroid Cancer (MTC) - Tissue	*RET* mutations (SNVs, MNVs, and deletions)	P160045/S031 (09/21/2022)
Oncomine Dx Target Test (Life Technologies Corporation)	Thyroid Cancer (TC) - Tissue	*RET* fusions	P160045/S031 (09/21/2022)
Oncomine Dx Target Test (Life Technologies Corporation)	Non-Small Cell Lung Cancer (NSCLC) - Tissue	*RET* fusions	P160045/S031 (09/21/2022)

Source: U.S. FDA List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools), Available at: https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

5 Nonclinical Pharmacology/Toxicology

5.1. 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.

5.2. 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 NSCLC indication.

5.3. Pharmacology

Not applicable. All relevant nonclinical information has been previously submitted. There is no new nonclinical information provided within this submission.

The FDA's Assessment:
Not applicable

5.4. ADME/PK

Not applicable. All relevant nonclinical information has been previously submitted. There is no new nonclinical information provided within this submission.

The FDA's Assessment:
Not applicable

5.5. Toxicology

Not applicable. All relevant nonclinical information has been previously submitted. There is no new nonclinical information provided within this submission.

The FDA's Assessment:
Not applicable

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

NDA 213246/S-011 is a labelling supplement for advanced or metastatic RET Fusion-Positive NSCLC, based on data from LIBRETTO-431 entitled "A Multicenter, Randomized, Open-Label, Phase 3 Trial Comparing Selpercatinib to Platinum-Based and Pemetrexed Therapy with or without Pembrolizumab as Initial Treatment of Advanced or Metastatic RET-Fusion Positive NSCLC".

The proposed indication received regular approval on Sep 21, 2022, after fulfillment of PMR 3829-2, based on data from Study LOXO-RET-17001 (LIBRETTO-001). The current submission based on data from LIBRETTO-431 provided additional evidence to support the use of selpercatinib for advanced or metastatic RET Fusion-Positive NSCLC. The proposed dosage is the same as the currently approved weight-based dosage (120 mg BID in patients less 50 kg, and 160 mg BID in patients 50 kg or more).

S-011 includes efficacy, safety and PK data from Study LIBRETTO-431 and an updated population pharmacokinetics (PopPK) and exposure-response (E-R) report (ELIL-PMX-SELPERCATINIB-5424, submitted on 02/20/2024 with a data cut-off 1 May 2023). The PopPK and E-R for safety results were generally consistent with previous submissions. An increased selpercatinib exposure was associated with a higher probability of ORR and there was no association between selpercatinib exposure and PFS. An increased risk of increased ALT, increased AST, hypertension, and hypersensitivity was not observed with higher selpercatinib exposure for all participants and for patients with NSCLC.

Recommendations: The Office of Clinical Pharmacology has reviewed the information contained in NDA 213246/S-011. The supplement is approvable from a clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

The PK of selpercatinib in patients, including those with NSCLC, has been well characterized using PK data from Study LIBRETTO-001.

A comprehensive summary of PK data from LIBRETTO-001 across all prior data cutoff dates was submitted in the sNDA to fulfill accelerated approval requirement related to the *RET* fusion-positive TC indication on 14 August 2023 (Sequence No. 0765).

New clinical pharmacology data related to LIBRETTO-431 are provided below, including a descriptive analysis of selpercatinib trough (predose) PK data for patients enrolled in LIBRETTO-431 (data cutoff date 01 May 2023).

Descriptive analysis for selpercatinib PK data

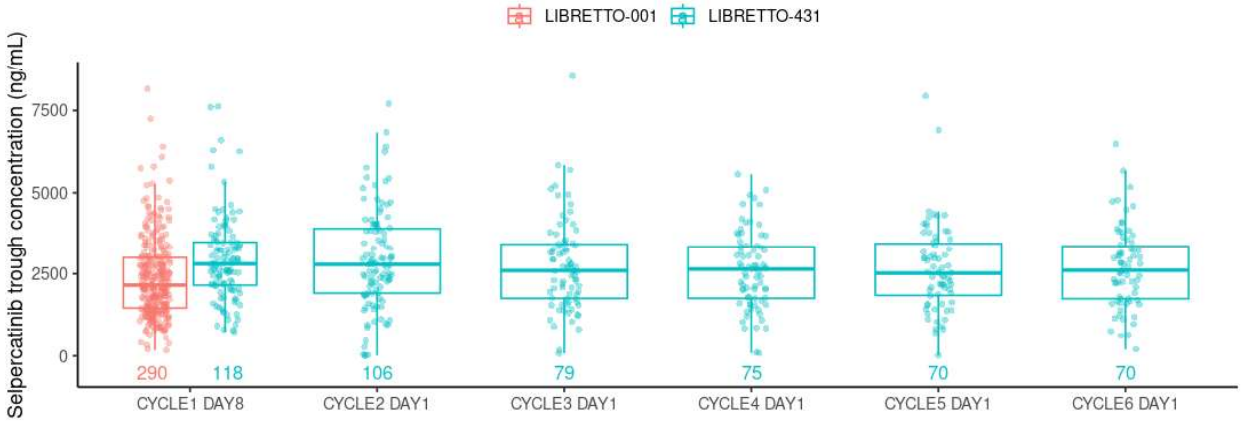
A descriptive analysis was conducted for selpercatinib predose PK data from LIBRETTO-431 patients with 160 mg BID (data cutoff date 01 May 2023).

In the **selpercatinib arm**, patients dosed with 160 mg BID had steady-state geometric mean C_{trough} which ranged from 2230 to 2670 ng/mL and geometric CV% in the range of 48% to 143% across visits.

For patients who were dosed with selpercatinib 160 mg BID after crossing over from the **control arm**, the steady-state geometric mean C_{trough} ranged from 1380 to 2520 ng/mL with geometric CV% from 47% to 293% across visits.

Overall, steady-state C_{trough} values were comparable across visits, regardless of whether they were in the **selpercatinib arm** or the **control arm** that crossed over to selpercatinib, due to the fact that the exposure ranges overlapped substantially across visits and between the 2 groups (Figure JZJC.5.7 of the LIBRETTO-431 CSR).

NSCLC patients dosed with 160 mg BID, steady-state C_{trough} in the **selpercatinib arm** of Study LIBRETTO-431 are comparable to C_{trough} observed from LIBRETTO-001 (Figure 6.1). Although steady-state geometric mean C_{trough} (Cycle 1 to Cycle 6) in NSCLC patients with 160 mg BID from **selpercatinib arm** of LIBRETTO-431 were 8% to 29% higher than that of NSCLC patients in LIBRETTO-001, their exposure ranges overlapped substantially.



Abbreviations: IQR = interquartile range; NSCLC = non-small cell lung cancer; PK = pharmacokinetic.
Note: Points represent the observed data. The solid line represents the median. The numbers below each box plots refer to the number of patients. The upper and lower ends of the "box" represent the 25th and 75th percentiles. The whiskers show the lowest data value still within 1.5 IQR of the lower quartile and the highest value still within 1.5 IQR of the upper quartile, where IQR is the interquartile range (the difference between the third and first quartiles, the middle 50%). Trough concentration is defined as the predose concentration of selpercatinib.

Figure 6.1. Comparison of steady-state trough PK concentrations for NSCLC patients with 160 mg twice daily in selpercatinib arm between LIBRETTO-431 and LIBRETTO-001.

Population PK modelling

A population PK and exposure-response analyses for efficacy and safety based on LIBRETTO-431 data will be conducted and provided as supportive information within 3 months of the sNDA submission date as agreed with FDA.

The Applicant's Position:

The steady-state C_{trough} from LIBRETTO-431 are similar to known PK data from LIBRETTO-001. Overall, the clinical pharmacology profile of selpercatinib is considered supportive of the dose regimen of 120 mg BID in patients weighing below 50 kg and 160 mg BID in patients who are at least above 12 years of age.

The FDA's Assessment:

FDA agrees that the PK of selpercatinib in patients, including those with NSCLC, are well characterized and the steady-state Ctrough from LIBRETTO-431 was within range of the that observed in LIBRETTO 001.

The updated population pharmacokinetics (PopPK) and exposure-response (E-R) report (ELIL-PMX-SELPERCATINIB-5424) submitted on 02/20/2024 showed generally consistent results compared to the previous submission and continues to support the currently approved weigh-based dosage (120 mg BID in patients less 50 kg, and 160 mg BID in patients 50 kg or more). See additional details in Appendix 19.4 and previous clinical pharmacology review for S-007 (09/06/2022, Ref ID 5041194), which supported the regular approval of the proposed indication for patients with advanced or metastatic RET Fusion-Positive NSCLC.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

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

The steady-state C_{trough} from LIBRETTO-431 is similar to known PK data from LIBRETTO-001 (Section 6.2.1).

The evidence of effectiveness and review of safety from Study LIBRETTO-431 in NSCLC patients is discussed in Section 8.2.

A population PK and exposure-response analyses for efficacy and safety based on LIBRETTO-431 data will be conducted and provided as supportive information within 3 months of the sNDA submission date as agreed with FDA.

The Applicant's Position:

The overall benefit-risk profile of LIBRETTO-431 is consistent with LIBRETTO-001.

Lilly continues to recommend using the weight-based dose regimen (that is, 120 mg BID in patients less 50 kg, and 160 mg BID in patients 50 kg or more).

The FDA's Assessment:

FDA agrees. See updated population PK and exposure-response analyses for efficacy and safety submitted during the review cycle in section 19.4.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

No new recommendation compared to the previous submission.

The FDA's Assessment:

Not applicable.

6.2.2.3. Outstanding Issues

The Applicant's Position:

None.

The FDA's Assessment:

Not applicable.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Please see Section 6.2.1.

The Applicant's Position:

No new recommendations compared to previous submission.

The FDA's Assessment:

Not applicable.

6.3.2. Clinical Pharmacology Questions

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

Data:

Not applicable.

The Applicant's Position:

The majority of studies in the clinical pharmacology program were conducted in healthy volunteers. The evidence of effectiveness from Study LIBRETTO-431 in NSCLC patients is discussed in Section 8.

The FDA's Assessment:

Not applicable.

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

Data:

Please see Section 6.2.1 and Section 6.2.2.

The Applicant's Position:

The Sponsor considers that the weight-based dosing regimen (120 mg BID in patients weighing below 50 kg and 160 mg BID in patients who are at least 50 kg) is still appropriate for patients with NSCLC.

The FDA's Assessment:

FDA agrees.

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

The Applicant's Position:

No new recommendations compared to the previous submission.

The FDA's Assessment:

Not applicable.

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 clinically relevant selpercatinib food-drug or drug-drug interactions.

(b) (4)

The Applicant's Position:

No new recommendations compared to previous the submission.

The FDA's Assessment:

Not applicable.

X	X
Primary Reviewer Miao Zhao	Team Leader Jeanne Fourie Zirkelbach

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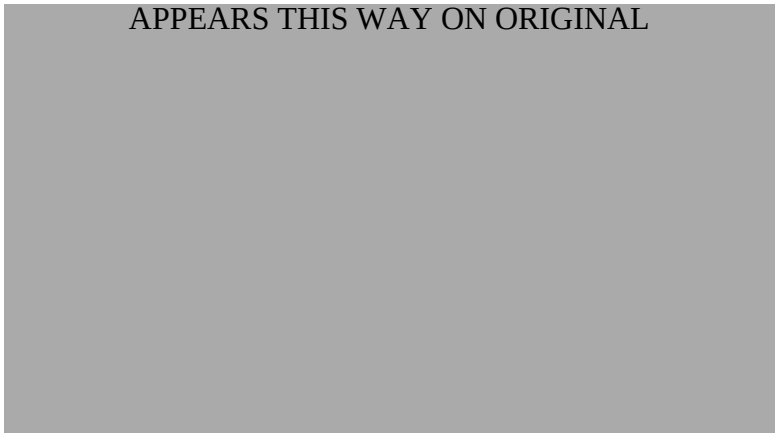

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 7.1 gives a brief overview of the LIBRETTO-431 study.

Table 7.1. Clinical Study Pertinent to the Claimed Indication

Study Identifier; Study Status; Participating Countries	Objective 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
A Multicenter, Randomized, Open-Label, Phase 3 Trial Comparing Selpercatinib to Platinum-Based and Pemetrexed Therapy with or without Pembrolizumab as Initial Treatment of Advanced or Metastatic *RET* Fusion-Positive NSCLC (LIBRETTO-431) Status: ongoing Countries (n=23): • North America	**Primary**: PFS per RECIST 1.1 by BICR **Secondary:** PFS per RECIST 1.1 by investigator, OS, ORR/DOR/DCR per RECIST 1.1 by BICR and investigator, PFS2, Time to CNS progression per RECIST 1.1. by BICR and Time to deterioration in pulmonary symptoms: cough, chest pain, and	A global, multicenter, randomized, open-label, controlled Phase 3 study of Oral Selpercatinib compared to Platinum-Based and Pemetrexed Therapy with or without Pembrolizumab in Patients with Advanced Solid Tumors or Metastatic *RET*	• Selpercatinib 160 mg BID, orally in continuous 21-day cycles. • Carboplatin: AUC 5 (maximum dose 750 mg); Day 1 Q3W for 4 cycles (IV) • Cisplatin: 75 mg/m^2, Day 1 Q3W for 4 cycles (IV) • Pemetrexed; 500 mg/m^2 (with vitamin supplementation), Day 1 Q3W (IV)	• Planned: 250 • Randomized (**ITT Population**): 261 • Randomized with the intent to receive pembrolizumab (**ITT-Pembrolizumab Population**): 212 • Treated (**Safety-Overall Population**): 256 • Treated with pembrolizumab (**Safety-Pembrolizumab Population**): 209	Study initiation: 19 March 2020 (first participant entered treatment) Data cutoff: 01 May 2023 (data cutoff date for the interim CSR)

Study Identifier; Study Status; Participating Countries	Objective 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
• South America • Europe • Asia Australia	dyspnea as measured by the NSCLC-SAQ	Fusion-Positive NSCLC	• Pembrolizumab (investigator's choice); 200 mg, Day 1 Q3W up to 35 cycles (IV)		

Abbreviations: AUC = area under the concentration versus time curve; BICR = blinded independent central review; BID = twice daily; CNS = central nervous system; CSR = clinical study report; DCR = disease control rate; DOR = duration of response; ITT = intent-to-treat; IV = intravenous; n = number of patients in the specified category; NSCLC = non-small cell lung cancer; NSCLC-SAQ = Non-Small Cell Lung Cancer Symptom Assessment Questionnaire; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; *RET* = REarranged during Transfection.

The Applicant's Position:

The primary study supporting the evaluation of efficacy in this sNDA is LIBRETTO-431. A detailed description of the results is provided in Section 8.

The FDA's Assessment:

FDA agrees with the Applicant's position that the primary study supporting the evaluation of efficacy in this sNDA is LIBRETTO-431, a multi-regional (excluding US), open-label, randomized, active-controlled trial of selpercatinib versus platinum-based and pemetrexed chemotherapy with or without pembrolizumab in patients with treatment-naïve RET fusion-positive, unresectable locally advanced or metastatic NSCLC.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. A Multicenter, Randomized, Open-Label, Phase 3 Trial Comparing Selpercatinib to Platinum-Based and Pemetrexed Therapy with or without Pembrolizumab as Initial Treatment of Advanced or Metastatic *RET* Fusion-Positive Non-Small Cell Lung Cancer (LIBRETTO-431)

Trial Design

The Applicant's Description:

LIBRETTO-431 is a global, multicenter, randomized, open-label, controlled Phase 3 study comparing selpercatinib to platinum-based and pemetrexed therapy with or without pembrolizumab in patients with advanced or metastatic, *RET* fusion-positive nonsquamous NSCLC.

Patients were stratified based on

- geography (East Asian versus non-East Asian)
- brain metastases per investigator assessment (presence versus absence or unknown), and
- investigator's choice of treatment with or without pembrolizumab. This decision must be determined at the time of randomization.

Adult patients with histologically confirmed, unresectable, locally advanced or metastatic nonsquamous NSCLC with no previous systemic therapy for metastatic disease were eligible.

After confirmation of eligibility, 261 patients were randomly assigned to treatment. Initially, patients were randomly assigned in a ratio of 1:1. Following the approval of Protocol Amendment (b), patients were randomly assigned in a ratio of 2:1, and as a result, the final randomization allocation was 1.6:1 to

- **selpercatinib arm**: treated with selpercatinib (160 mg BID continuously in 21-day cycles), or
- **control arm**: treated with pemetrexed (500 mg/m^2 intravenous) Q3W plus the investigator's discretion of the following treatments administered Q3W:
  - 4 cycles of carboplatin (area under the plasma concentration-time curve 5, maximum dose of 750 mg intravenous) or cisplatin (75 mg/m^2 intravenous), and
  - with or without pembrolizumab (200 mg intravenous) up to 35 cycles.

After the completion of 4 cycles of chemotherapy without progressive disease, patients randomly assigned to the **control arm** received maintenance therapy with pemetrexed (500 mg/m^2) with or without pembrolizumab (200 mg) Q3W according to the decision made at the time of randomization. Patients with the intent by the investigator to be treated without pembrolizumab were restricted to no more than 20%. Treatment continued until radiographic disease progression confirmed by BICR, unacceptable toxicity, withdrawal of consent, or death.

Patients randomly assigned to the **control arm** who discontinued treatment for radiographic disease progression that was confirmed by BICR may have been eligible for crossover to selpercatinib which was optional at the discretion of the investigator.

The primary endpoint of PFS per RECIST 1.1 by BICR was tested sequentially in 2 populations: **ITT-Pembrolizumab Population** followed by the **ITT Population**.

The FDA's Assessment:

In general, FDA agrees with the descriptions of the trial design of LIBRETTO-431 (NCT04194944), a multicenter, open-label, active-controlled, randomized trial which evaluated selpercatinib compared to platinum-based and pemetrexed chemotherapy with or without pembrolizumab in patients with *RET* fusion-positive, unresectable locally advanced or metastatic NSCLC with no previous systemic therapy for metastatic disease.

Patients (N=261) were randomized to receive either selpercatinib (160 mg orally twice daily) in continuous 21-day cycles or pemetrexed intravenously (IV) (500 mg per square meter of body-surface area) along with the investigator's choice of platinum therapy (carboplatin IV [AUC 5, maximum dose 750 mg] or cisplatin IV [75 mg per square meter]) with or without pembrolizumab IV (200 mg) every 21 days. Treatment continued until disease progression or unacceptable toxicity. Crossover from the control arm to selpercatinib was permitted following disease progression. Patients were stratified according to geographic region (East Asia vs. elsewhere), brain metastases at baseline (presence vs. absence or unknown), and the investigator's intent (before randomization) to treat the patient with or without pembrolizumab. Tumor assessments were performed every 6 weeks for two assessments, then every 9 weeks for four assessments, and then every 12 weeks thereafter.

Patients were initially randomized to 1:1 ratio in the trial; however, with Amendment (b), which was enacted three months after the first patient was enrolled, the protocol was modified to revise the randomization ratio to a 2:1 ratio to minimize the number of patients treated in the control arm based on existing efficacy data for selpercatinib in ongoing clinical trials (primarily LIBRETTO-001, an ongoing international single-arm trial of selpercatinib in patients with *RET* fusion-positive advanced solid tumors). This

change was made prior to the conduct of any interim analyses.

Since randomization was stratified by investigator's choice of treatment with or without pembrolizumab, it is reasonable to conduct the primary efficacy analysis in a subpopulation defined by this stratification factor, i.e., ITT-Pembrolizumab Population.

For the potential impact of the change of randomization ratio on the efficacy outcome, please refer to FDA comments under section "Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)." below.

Eligibility Criteria

The Applicant's Description:

- Patients were eligible if they had
  - histologically or cytologically confirmed Stage IIIB-IIIC or Stage IV NSCLC that was not suitable for radical surgery or radiation therapy
  - *RET* gene fusion in tumor using polymerase chain reaction or NGS (results in blood using NGS were also acceptable)
  - measurable disease per RECIST 1.1 as assessed by investigator, or
  - an ECOG PS score of 0 to 2.
- Patients were excluded if they
  - had additional validated oncogenic drivers in NSCLC, if known
  - had symptomatic CNS metastases, carcinomatous meningitis, or untreated spinal cord compression
  - had clinically significant active cardiovascular disease or history of myocardial infarction within 6 months or QTcF greater than 470 msec
  - had uncontrolled, disease-related, pericardial effusion or pleural effusion
  - had prior systemic therapy (chemotherapy, immunotherapy, or biological therapy) for metastatic disease, or
  - were taking a concomitant medication known to cause QTc prolongation.
- Patients who the investigator planned on treating with pembrolizumab if randomly assigned to control were also excluded if they had
  - a history of interstitial lung disease or interstitial pneumonitis
  - active autoimmune disease or any illness or treatment that could compromise the immune system, or
  - used escalating or chronic supraphysiologic doses of corticosteroids or immunosuppressive agents.

The FDA's Assessment:
FDA agrees with the Applicant's description of eligibility criteria.

In addition, patients were required to be at least 18 years of age. Patients who received adjuvant or neoadjuvant therapy were eligible if the last dose of the systemic treatment was completed at least 6 months prior to randomization.

Regarding the identification of a *RET* fusion, results should have been generated from a laboratory with CLIA, ISO/IEC, CAP, or other similar certification that clearly denotes the presence of a RET alteration. In all cases, the presence of the RET fusion was to be confirmed upon review of the pathology report by the Applicant or designee prior to enrollment.

Study Endpoints

The Applicant's Description:

In LIBRETTO-431, the primary endpoint is PFS per RECIST 1.1 as assessed by the BICR.

OS was selected as the error-controlled, adequately powered, key secondary endpoint, and was tested conditionally only on achieving statistical significance for PFS.

Secondary endpoints include ORR and DOR by BICR assessment, and ORR, DOR, and time to CNS progression for patients with CNS metastases.

Analyses Sets

The analyses populations used to describe the data are

- **ITT Population:** All randomized patients, even if a patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Patients will be analyzed according to the treatment arm they were assigned to regardless of what actual treatment they receive
- **ITT-Pembrolizumab Population:** Patients included in the **ITT Population** who were stratified with the intent to receive pembrolizumab in the event of the **control-arm** assignment
- **Safety-Overall Population:** All randomized patients who take at least 1 dose (including a partial dose) of study treatment. Analysis of safety data will be based on the actual treatment a patient received on the first study treatment administration regardless of which treatment they were randomized to receive ("as treated")

- **Safety-Pembrolizumab Population:** Randomized patients stratified to investigator's ITT with pembrolizumab, and who received at least 1 dose (including a partial dose) of selpercatinib; and all randomized patients who took at least 1 dose (including a partial dose) of pembrolizumab. Analysis of safety data was based on the actual treatment a patient received on the first study treatment administration regardless of which treatment they were randomized to receive ("as treated").

Efficacy data presented in this assessment aid and the Clinical Overview are based on the **ITT-Pembrolizumab Population**, except for

- the primary endpoint, and OS which are based on both the **ITT-Pembrolizumab Population** and the **ITT Population**, and
- protocol deviations, which are based on the **ITT Population**.

Overall, the efficacy findings in the **ITT-Pembrolizumab** and the **ITT Populations** were similar unless specifically stated.

For the description of the safety data, the **Safety-Overall Population** is used.

The FDA's Assessment:

In general, FDA agrees with the Applicant's descriptions of the trial endpoints and analyses populations, as presented in this section. The primary endpoint in trial LIBRETTO-431 was PFS per RECIST 1.1 as assessed by the BICR in the ITT-Pembro population (as defined above). One interim analysis of PFS for efficacy was planned after 67% information fraction (93 PFS events) observed in the ITT-Pembro population. The final analysis was planned after 140 BICR-assessed PFS events observed in the ITT-Pembro population. The O'Brien-Fleming method was used for the alpha allocation at the time of the interim and final analyses of the primary endpoint of PFS in the ITT-Pembro population. PFS per RECIST 1.1 as assessed by the BICR in the ITT population was planned to be hierarchically tested if PFS in the ITT-Pembro population was statistically significant.

OS in the ITT population was a key secondary endpoint in trial LIBRETTO-431 and was planned to be tested hierarchically if PFS according to BICR was statistically significant in both the ITT-Pembro population and the ITT population. FDA considered results from other endpoints, such as ORR, DOR, time to CNS progression, that were not included as part of a formal testing plan, to be descriptive only.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The protocol, located in an appendix (Protocol and addenda) and the SAPs appendix (Statistical methods) of the CSR provide the study's planned analyses, comparisons, statistical tests, and determination of sample size.

SAP version 1 was approved on 23 October 2019, prior to the first patient visit.

SAP version	Date	Change and key drivers of the change
Version 2 (prior to 1st database lock)	29 July 2020	Updated objectives, endpoints, study design and statistical hypothesis with intent to receive pembrolizumab according to Protocol Amendment (c). Added definitions of **ITT-pembrolizumab** and **Safety-pembrolizumab populations**. Added definitions of DCR, PFS2, ORR, and DOR. Modified subgroups analyses to investigator's choice of treatment with pembrolizumab as the primary analysis set.
Version 3	03 October 2022	Added endpoints of intracranial response and time to CNS progression. Per Protocol Amendment (d) added that the study was to be considered positive if a statistically significant improvement in PFS by BICR in the **ITT-pembrolizumab population** was observed. Replace "co-primary" with "primary" endpoint. Added definitions for crossover and brain/CNS tumors, crossover baseline measurements, and sensitivity analyses. Updated definitions of TEAEs, BOR, CBR, DCR, PFS2 and AESIs.

Abbreviations: AESIs = adverse events of special interest; BICR = blinded independent central review; BOR = best overall response; CBR = clinical benefit rate, CNS = central nervous system; DCR = disease control rate; DOR = duration of response; ITT = intent to treat; ORR = objective response rate; PFS = progression-free survival; PFS2 = progression-free survival 2; SAP = statistical analysis plan; TEAEs = treatment -emergent adverse events.

The FDA's Assessment:

FDA agrees with the Applicant's descriptions of the amendments of the statistical analysis plan of trial LIBRETTO-431.

Protocol Amendments

The Applicant's Description:

Table 8.1 outlines the dates of the protocol amendments along with the key drivers of each amendment. This interim report provides information on study conduct from the

original protocol (dated 27 June 2019) up to and including Protocol Amendment (d) (18 November 2020).

Table 8.1. Protocol Amendment History

Document Amendment	Date	Key Drivers of the Amendment
Amendment (a)	07 November 2019	This amendment incorporates changes requested by regulatory agencies and included but were not limited to changes to the eligibility criteria, objectives, dose adjustment, and biomarker sections.
Amendment (b)	10 June 2020	This amendment incorporates changes to the primary endpoint, sample size, and randomization ratio based on emerging data from Phase 1/2 Study LIBRETTO-001 and to satisfy certain country-specific regulatory and payer expectations.
Amendment (c)	26 June 2020	This amendment corrects typographical errors and inconsistencies that were noted in Study J2G-MC-JZJC amendment (b) that impacted the study analysis.
Amendment (d)	18 November 2020	This amendment incorporates changes to include additional endpoints to further characterize the intracranial activity of **selpercatinib arm** compared to the **control arm**.

The FDA's Assessment:

In general, FDA agrees with the Applicant's descriptions of the protocol amendments of trial LIBRETTO-431. The protocol amendments did not have an impact on the integrity of the trial or interpretation of the results.

8.1.2. 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 on Harmonization GCP Guidelines, and
- applicable laws and regulations.

The Applicant's Position:

LIBRETTO-431 was conducted in compliance with GCP.

The FDA's Assessment:

The Applicant's statement that Study LIBRETTO-431 was conducted in accordance with Good Clinical Practice (GCP) guidelines was reviewed in the CSR.

Financial Disclosure

Data:

The Sponsor is submitting documentation listing of all principal investigators and sub-investigators who participated at sites that randomized patients in the study, LIBRETTO-431, included in the sNDA submission. The listing indicates whether the investigators have provided a financial disclosure Certification (Form FDA 3454). None of the investigators or sub-investigators in LIBRETTO-431 met the threshold for a Disclosure statement (Form FDA 3455).

The Applicant's Position:

As this is a multi-site, multi-national study (patients were enrolled across 23 countries in North America, South America, Europe, Asia, and Australia) and the primary endpoint is assessed by a BICR, 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.

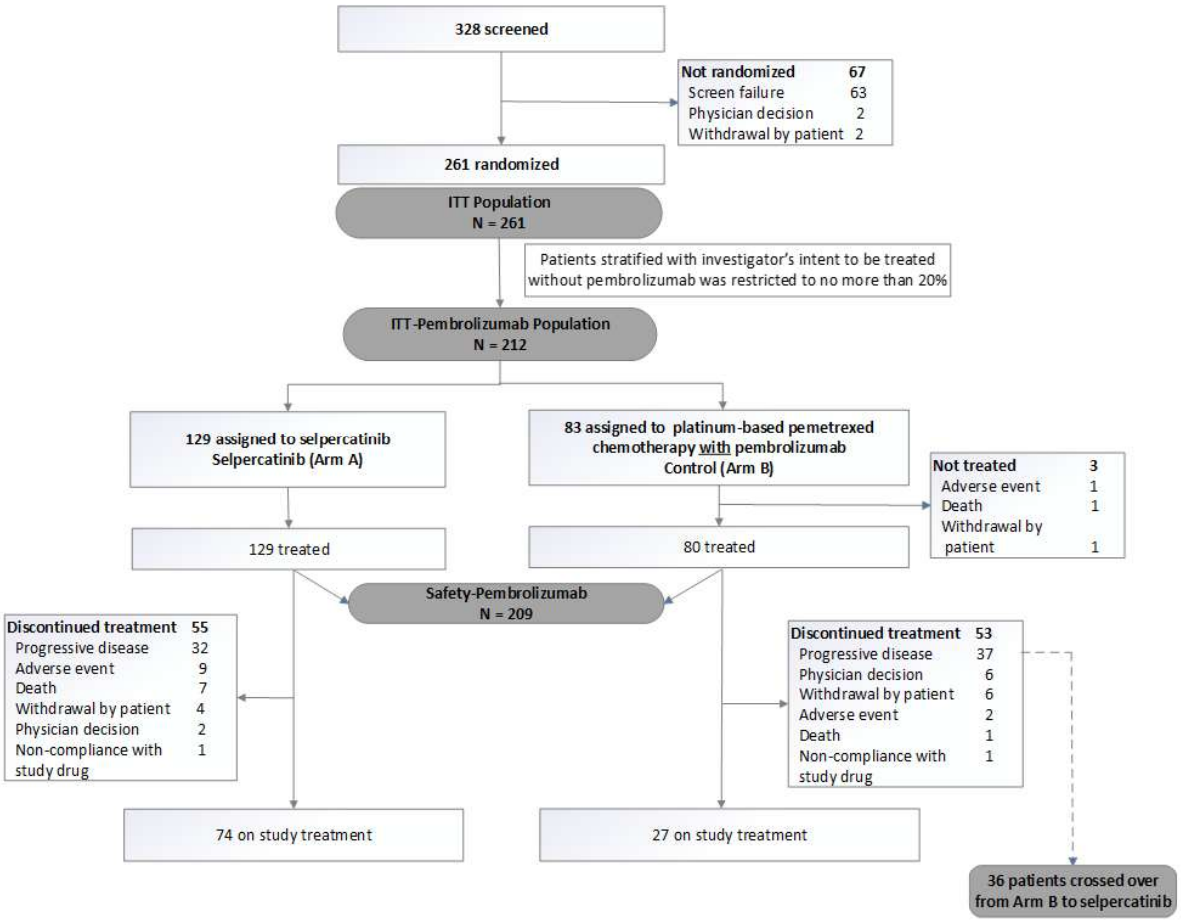
Patient Disposition

Data:

Figure 8.1 presents the disposition of patients for the **ITT-Pembrolizumab Population**.

The **ITT-Pembrolizumab Population** consisted of 212 patients randomly assigned to either the **selpercatinib arm** (N = 129) or the **control arm** (N = 83).

As of the data cutoff date, 209 patients were treated in the **ITT-Pembrolizumab Population**.



Abbreviations: ITT = intent-to-treat; **ITT-Pembrolizumab Population** = patients included in the **ITT Population** who were stratified with the intent to receive pembrolizumab in the event of the **control-arm** assignment *RET*-altered other cancers; N = total number of patients in the population.
Data cutoff date: 01 May 2023

Figure 8.1. Study patient disposition for the ITT-Pembrolizumab Population.

The Applicant's Position:

The patient disposition for the **ITT-Pembrolizumab Population** and **ITT Population** is similar.

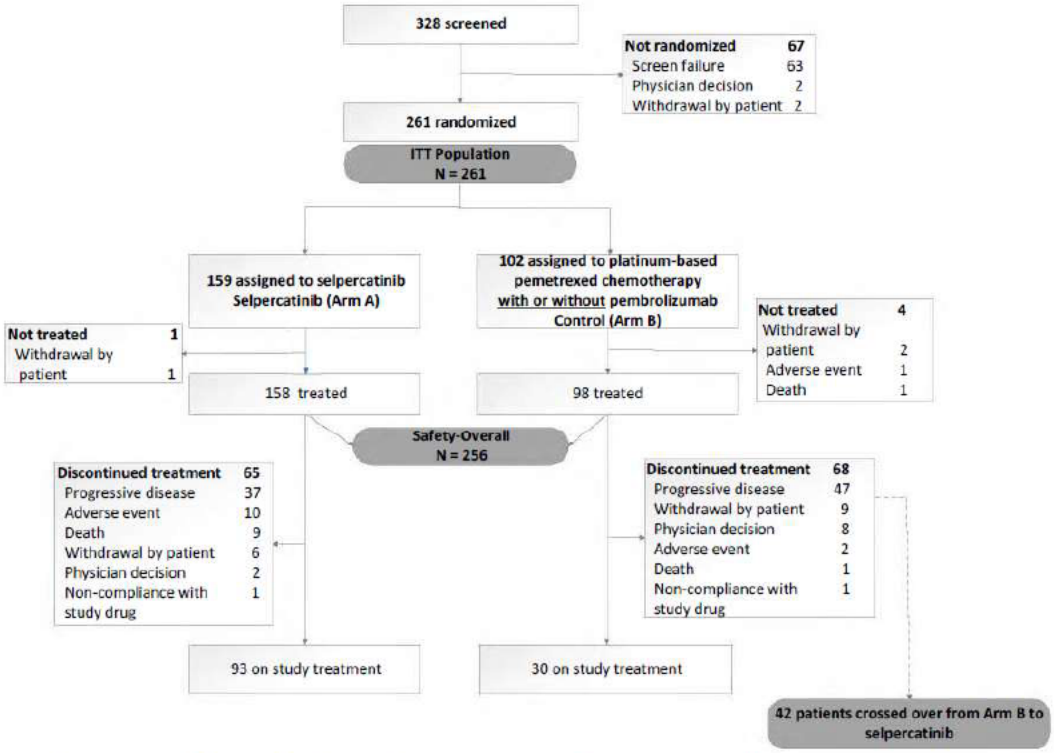
The FDA's Assessment:

FDA agrees that the patient disposition for the two populations is similar (Figure 8.1 and Figure 8.2). There was limited withdrawal before treatment initiation; in the selpercatinib

arm, 1 patient chose to withdraw; in the control arm, 4 patients withdrew (2 withdrawals by patient, 1 patient had an adverse event, and 1 patient died). The most common reason for treatment discontinuation in both arms was progressive disease, followed by adverse event/death in the selpercatinib arm vs. withdrawal by patient/physician decision in the control arm.

In the overall **ITT population**, a total of 261 patients were enrolled in LIBRETTO-431 with 159 patients assigned to the selpercatinib arm and 102 patients assigned to the control arm.

With respect to the **ITT-pembro population**, a total of 212 patients were enrolled with an intent to treat with pembrolizumab if randomized to the control arm, with 129 patients assigned to the selpercatinib arm and 83 patients assigned to the chemotherapy with pembrolizumab arm. Of note, data on investigator rationale for decision to intent to treat with or without pembrolizumab were not collected on an individual patient level.



Abbreviations: ITT = intent-to-treat; N = number of patients in analysis population.

Study patient disposition figure for ITT Population.

Figure 8.2: Study patient disposition for the ITT Population, DCO 05/01/2023 (Source: CSR for Study LIBRETTO-431, page 161)

Protocol Violations/Deviations

Data:

Important protocol deviations were defined as any deviation from the protocol that could potentially impact the study assessment, patient rights, and the study integrity.

A protocol deviation related to the randomization ratio was confirmed to be a serious breach of rights of trial patients. The trial's initial 1:1 randomization ratio was updated to a 2:1 randomization ratio beginning in Protocol Amendment (b). It was subsequently uncovered that a subset of patients enrolled under Amendment (b) or subsequent amendments, while informed in the informed consent document to have 2 chances out of 3 to receive selpercatinib, was in fact randomized with 1 chance out of 2. This was caused by a delay in updating the randomization ratio in the interactive web response system. The incorrect randomization ratio information affected 56 patients in 13 countries. An evaluation determined that although there was a significant impact to patient's rights, there was no risk to patient safety, study data integrity, or impact to the overall study analysis.

Table 8.2 present a summary of important protocol deviations for the **ITT Population**.

Table 8.2. Summary of Important Protocol Deviations
ITT Population
Core Study Period

Protocol Deviation Category Study Specific Deviation Term	Selpercatinib (N=159) n (%)	Carboplatin or Cisplatin + Pemetrexed +/- Pembrolizumab (N=102) n (%)	Total (N=261) n (%)
Subjects with >=1 Important Protocol Deviation	73 (45.9)	39 (38.2)	112 (42.9)
Protocol Deviation	73 (45.9)	39 (38.2)	112 (42.9)
Study Procedure Compliance	35 (22.0)	28 (27.5)	63 (24.1)
Concomitant Medication	16 (10.1)	1 (1.0)	17 (6.5)
Investigational Medicinal Product and/or Investigational Device	15 (9.4)	3 (2.9)	18 (6.9)
Informed Consent	8 (5.0)	3 (2.9)	11 (4.2)
Eligibility Criteria	6 (3.8)	6 (5.9)	12 (4.6)
Safety Reporting	5 (3.1)	4 (3.9)	9 (3.4)
Treatment Assignment/Randomization	3 (1.9)	0	3 (1.1)
Discontinuation Criteria	2 (1.3)	1 (1.0)	3 (1.1)

Cutoff Date: 2023-05-01.
Abbreviations : N = number of Subjects in the analysis population; n = number of Subjects in the specified category.
Percentages are based on the treatment column denominator, N.

Program Location: /lillyce/prd/ly3527723/j2g_mc_jzjc/csr1/programs/primary/tfl/t_pd_itt.sas
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Table 14.3.8: Summary of Important Protocol Deviations — page 2 of 2
ITT Population — 03:25 05OCT2023
J2G-MC-JZJC Crossover Phase — PDPM

Protocol Deviation Category Study Specific Deviation Term	Selpercatinib (N=42) n (%)
Subjects with >=1 Important Protocol Deviation	13 (31.0)
Protocol Deviation	13 (31.0)
Study Procedure Compliance	8 (19.0)
Informed Consent	3 (7.1)
Safety Reporting	2 (4.8)
Concomitant Medication	1 (2.4)
Investigational Medicinal Product and/or Investigational Device	1 (2.4)

Cutoff Date: 2023-05-01.
Abbreviations : N = number of Subjects in the analysis population; n = number of Subjects in the specified category.
Percentages are based on the treatment column denominator, N.

Program Location: /lillyce/prd/ly3527723/j2g_mc_jzjc/csr1/programs/primary/tfl/t_pd_itt.sas
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Data Location: /lillyce/prd/ly3527723/j2g_mc_jzjc/csr1/data/analysis/restricted/adsl, addv

The Applicant's Position:

The protocol deviations that occurred were reviewed by the Sponsor and considered unlikely to have substantially 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 study procedures and concomitant medications. These deviations are unlikely to have a significant impact on study results.

Table of Demographic Characteristics

Data:

Table 8.3 presents the demographic summary for the **ITT-Pembrolizumab Population**.

Table 8.3 Demographic Summary
ITT-Pembrolizumab Population

Demographic Parameter		Selpercatinib (N=129)	Carboplatin or Cisplatin +Pemetrexed +Pembrolizumab (N=83)	Total (N=212)
Sex n(%)	n*a	129	83	212
	Female	65 (50.4)	48 (57.8)	113 (53.3)
	Male	64 (49.6)	35 (42.2)	99 (46.7)
Age (yrs)	n*a	129	83	212
	Mean (SD)	59.8 (11.1)	60.2 (11.8)	60.0 (11.3)
	Median	60.0	62.0	61.5
	Min - Max	31 - 84	31 - 83	31 - 84
Age categories n(%)	n*a	129	83	212
	<65	82 (63.6)	49 (59.0)	131 (61.8)
	>=65	47 (36.4)	34 (41.0)	81 (38.2)
Race n(%)	N*a	129	79	208
	American Indian or Alaska Native	2 (1.6)	1 (1.3)	3 (1.4)
	Asian	76 (58.9)	41 (51.9)	117 (56.3)
	Black or African American	2 (1.6)	0	2 (1.0)
	Native Hawaiian or Other Pacific Islander	0	0	0
	White	49 (38.0)	37 (46.8)	86 (41.3)
	Missing	0	4	4
Ethnicity n(%)	N*a	4	5	9
	Hispanic or Latino	0	0	0
	Not Hispanic or Latino	4 (100.0)	5 (100.0)	9 (100.0)
	Not reported	0	0	0
	Missing	125	78	203

Cutoff Date: 2023-05-01.
Abbreviations: N = number of subjects in analysis population; n = number of subjects;
SD = Standard Deviation; Min = Minimum; Max = Maximum
Note: number of subjects with non-missing data, used as denominator.
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Table 14.1.4.1.1.2: Demographics Summary
ITT-Pembrolizumab Population
J2G-MC-JZJC

Demographic Parameter		Selpercatinib (N=129)	Carboplatin or Cisplatin +Pemetrexed +Pembrolizumab (N=83)	Total (N=212)
Weight (kg)	n*a	129	83	212
	Mean (SD)	67.1 (15.3)	67.9 (15.2)	67.4 (15.2)
	Median	65.4	65.0	65.2
	Min - Max	42 - 136	42 - 115	42 - 136
Height (cm)	n*a	128	83	211
	Mean (SD)	164.6 (9.4)	164.4 (9.2)	164.5 (9.3)
	Median	164.0	163.0	164.0
	Min - Max	146 - 184	146 - 185	146 - 185
BMI (kg/m^2)	n*a	128	83	211
	Mean (SD)	24.63 (4.49)	24.96 (4.37)	24.76 (4.44)
	Median	23.76	24.69	24.27
	Min - Max	16.4 - 43.7	17.3 - 38.6	16.4 - 43.7
Country n(%)	n*a	129	83	212
	Argentina	2 (1.6)	0	2 (0.9)
	Australia	2 (1.6)	2 (2.4)	4 (1.9)
	Belgium	2 (1.6)	1 (1.2)	3 (1.4)
	Brazil	7 (5.4)	1 (1.2)	8 (3.8)
	Canada	1 (0.8)	0	1 (0.5)
	China	55 (42.6)	27 (32.5)	82 (38.7)
	Czech Republic	0	1 (1.2)	1 (0.5)
	France	0	3 (3.6)	3 (1.4)
	Germany	4 (3.1)	4 (4.8)	8 (3.8)
	Greece	2 (1.6)	0	2 (0.9)

Cutoff Date: 2023-05-01.
Abbreviations: N = number of subjects in analysis population; n = number of subjects;
SD = Standard Deviation; Min = Minimum; Max = Maximum
Note: number of subjects with non-missing data, used as denominator.

Program Location: /lillyce/prd/ly3527723/j2g_mc_jzjc/csr1/programs/primary/tfl/t_demo_ittp.sas
Output Location: /lillyce/prd/ly3527723/j2g_mc_jzjc/csr1/output/restricted/t_14_1_4_1_1_2.rtf
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Table 14.1.4.1.1.2: Demographics Summary
ITT-Pembrolizumab Population 04:04 02AUG2023
J2G-MC-JZJC PDPM

Demographic Parameter		Selpercatinib (N=129)	Carboplatin or Cisplatin +Pemetrexed +Pembrolizumab (N=83)	Total (N=212)
Country n(%)	Hong Kong	3 (2.3)	1 (1.2)	4 (1.9)
	Israel	1 (0.8)	2 (2.4)	3 (1.4)
	Italy	15 (11.6)	11 (13.3)	26 (12.3)
	Japan	8 (6.2)	2 (2.4)	10 (4.7)
	Korea, Republic of	8 (6.2)	7 (8.4)	15 (7.1)
	Mexico	3 (2.3)	1 (1.2)	4 (1.9)
	Netherlands	1 (0.8)	1 (1.2)	2 (0.9)
	Poland	0	1 (1.2)	1 (0.5)
	Russian Federation	1 (0.8)	2 (2.4)	3 (1.4)
	Spain	6 (4.7)	7 (8.4)	13 (6.1)
	Taiwan	1 (0.8)	4 (4.8)	5 (2.4)
	Turkey	7 (5.4)	0	7 (3.3)
	Ukraine	0	5 (6.0)	5 (2.4)
Region n(%)	n*a	129	83	212
	East Asia	75 (58.1)	41 (49.4)	116 (54.7)
	Non-East Asia	54 (41.9)	42 (50.6)	96 (45.3)

Cutoff Date: 2023-05-01.
Abbreviations: N = number of subjects in analysis population; n = number of subjects;
SD = Standard Deviation; Min = Minimum; Max = Maximum
Note: number of subjects with non-missing data, used as denominator.
Program Location: /lillyce/prd/ly3527723/j2g_mc_jzjc/csr1/programs/primary/tfl/t_demo_ittp.sas
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Data Location: /lillyce/prd/ly3527723/j2g_mc_jzjc/csr1/data/analysis/restricted/adsl

The Applicant's Position:

Baseline demographic characteristics for patients in the **ITT-Pembrolizumab Population** were generally well balanced across arms, although more East Asian patients were enrolled in the **selpercatinib arm** compared with the **control arm** (58.1% versus 49.4%, respectively).

The demographics in the **ITT Population** were consistent with those in the **ITT-Pembrolizumab Population**.

The FDA's Assessment:

FDA agrees with the Applicant's description of the baseline demographic characteristics of patients in trial LIBRETTO-431. The median age of patients was similar in the selpercatinib and control arms (60 and 62 years old, respectively), with a slight female predominance, which is consistent with prior studies of *RET* fusion-positive NSCLC (Hess et al, 2021; Lin et al, 2015).

LIBRETTO-431 was a multi-regional trial enrolled which enrolled patients in Europe (Argentina, Belgium, Czech Republic, France, Germany, Greece, Italy, Netherlands, Poland, Spain, Ukraine, Turkey), South America (Brazil), North America (Canada, Mexico), Australia, and Asia (China, Hong Kong, Israel, Japan, Korea, Russia, Taiwan). There was no US enrollment as LIBRETTO-431 began enrollment in March 2020 and selpercatinib received accelerated approved for treatment-naïve *RET* fusion-positive NSCLC in May 2020.

More than half of patients were enrolled in East Asia and ethnicity was not reported in the majority of patients. Overall FDA assessed that given the multiregional nature and design of the trial, disease and demographic characteristics of the patients enrolled, and standards of care across represented regions, the results of the trial could be applicable to US patients.

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

Data:

Overall, baseline disease characteristics and the distribution of *RET* fusion partners were well balanced between treatment arms.

The key prognostic factors of smoking status, ECOG, and the presence of brain metastases were similar between the **selpercatinib arm** and the **control arm**.

In the **ITT-Pembrolizumab Population**

- 32.1% were current or former smokers (**selpercatinib arm** 34.1% versus **control arm** 28.9%)
- 3.3% had an ECOG PS score of 2 (**selpercatinib arm** 2.3% versus **control arm** 4.8%)
- 93.4% had Stage IVA or IVB disease (**selpercatinib arm** 94.6% versus **control arm** 91.6%), and
- 20.3% had investigator-assessed CNS metastases (**selpercatinib arm** 19.4% versus **control arm** 21.7%).

In the **ITT-Pembrolizumab Population**, more patients in the **selpercatinib arm** were PD-L1 negative (24.0%) compared to the **control arm** (14.5%). PD-L1 status was not required and only collected if known. Slightly more patients in the **control arm** had missing PD-L1 status (38.6%) compared to the **selpercatinib arm** (33.3%).

The majority of *RET* fusions in the **ITT-Pembrolizumab Population** was identified by next-generation sequencing (60.4%), and the most common *RET* fusion partners were *KIF5B* (44.8%) and CCDC6 (9.9%). Additionally, 39.6% of *RET* fusions were identified by polymerase chain reaction, which did not specify the *RET* fusion partner. Patients submitted archival tissue samples, if available, for a retrospective central analysis of *RET* fusion status using the ODxTT. The number of patients with samples collected for **ITT-Pembrolizumab Population** was 93 (43.9%). In the **ITT-Pembrolizumab Population**, the positive percent agreement was 88% among 60 samples that met testing quality criteria.

*Prior anticancer treatment in the **ITT-Pembrolizumab Population***

Patients were not permitted to receive prior systemic therapy for metastatic disease, but local palliative treatment or neoadjuvant/adjuvant treatment for prior early-stage disease was permitted, provided it was completed prior to the protocol-defined timelines. A total of 31.1% patients received prior treatment (radiation, surgery, or systemic treatment for early-stage disease).

A total of 5.7% of patients (**selpercatinib arm** 3.9% versus **control arm** 8.4%) received prior adjuvant or neoadjuvant treatment for early-stage disease. Per protocol, it was completed more than 6 months prior to start of therapy and only 1 patient (on selpercatinib) had prior immunotherapy (durvalumab) as part of the adjuvant regimen.

The Applicant's Position:

In the **ITT-Pembrolizumab Population**, the key prognostic factors of smoking status, ECOG, and presence of brain metastases were similar between the **selpercatinib arm** and **control arm**. Baseline demographic characteristics for patients in the **ITT-Pembrolizumab Population** were generally well balanced across arms, although

more East Asian patients were enrolled in the **selpercatinib arm** compared with the **control arm** (58.1% versus 49.4%, respectively). Baseline data for the **ITT Population** were consistent with those in the **ITT-Pembrolizumab Population**.

The FDA's Assessment:

In general, FDA agrees with the Applicant's descriptions of the other baseline characteristics, including disease characteristics, of patients in trial LIBRETTO-431 as presented in this section. Key baseline disease characteristics are summarized in Table 8.4.

Most patients were non-smokers and had a high ECOG performance status. Approximately 20% of patients had known brain metastases. PD-L1 status was variable with one-third of patients missing this information. The most common *RET* fusion partners were KIF5B-RET and CCDC6-RET, similar to the fusion partners observed in patients with NSCLC in the initial single-arm Study LIBRETTO-001.

Table 8.4: Summary of Baseline Disease Characteristics

Parameter	Selpercatinib (N=129)	Carboplatin or Cisplatin +Pemetrexed +Pembrolizumab (N=83)	Total (N=212)
Study Entry Pathological Diagnosis Disease Stage, n (%)			
STAGE IIIB	7 (5.4)	5 (6.0)	12 (5.7)
STAGE IIIC	0	2 (2.4)	2 (0.9)
STAGE IVA	51 (39.5)	35 (42.2)	86 (40.6)
STAGE IVB	71 (55.0)	41 (49.4)	112 (52.8)
PD-L1 status, n (%)			
Negative	31 (24.0)	12 (14.5)	43 (20.3)
Positive	55 (42.6)	39 (47.0)	94 (44.3)
POSITIVE (>1%)	8 (6.2)	8 (9.6)	16 (7.5)
POSITIVE (LOW EXPRESSION TPS = 1-49%)	25 (19.4)	17 (20.5)	42 (19.8)
POSITIVE (HIGH EXPRESSION TPS = >=50%)	22 (17.1)	14 (16.9)	36 (17.0)
Missing	43 (33.3)	32 (38.6)	75 (35.4)
RET fusion result			
Positive (fusion partner not recorded)	58 (45.0)	31 (37.3)	89 (42.0)

Parameter	Selpercatinib (N=129)	Carboplatin or Cisplatin +Pemetrexed +Pembrolizumab (N=83)	Total (N=212)
KIF5B-RET	54 (41.9)	41 (49.4)	95 (44.8)
CCDC6-RET	13 (10.1)	8 (9.6)	21 (9.9)
NCOA4-RET	0	1 (1.2)	1 (0.5)
KIF13A-RET	0	1 (1.2)	1 (0.5)
KIAA1549L-RET	1 (0.8)	0	1 (0.5)
KIAA1468-RET	1 (0.8)	0	1 (0.5)
PRKAR1A-RET	0	1 (1.2)	1 (0.5)
OTHER*a	2 (1.6)	0	2 (0.9)
Tobacco Use			
Current	4 (3.1)	2 (2.4)	6 (2.8)
Former	40 (31.0)	22 (26.5)	62 (29.2)
Never	85 (65.9)	59 (71.1)	144 (67.9)
Baseline ECOG			
0	45 (34.9)	27 (32.5)	72 (34.0)
1	81 (62.8)	52 (62.7)	133 (62.7)
2	3 (2.3)	4 (4.8)	7 (3.3)
Presence of brain metastases			
No/Unknown	104 (80.6)	65 (78.3)	169 (79.7)
Yes	25 (19.4)	18 (21.7)	43 (20.3)

*a - Subjects with multiple RET results: KIF5B-RET and CDKAL1-RET, NCOA4-RET and ZNF32-AS3-RET.

Source: Adapted from Table JZJZ.4.5, LIBRETTO-431 CSR, page 86-89

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment duration in the Safety-Overall Population

The median duration of treatment in the core study period was as follows:

- **selpercatinib arm** exposure: 16.7 months, and
- **control arm** exposure: 9.8 months (any drug)
  - 10.0 months for pembrolizumab
  - 7.0 months for pemetrexed
  - 2.8 months for cisplatin, and

- 2.8 months for carboplatin.

Per protocol, cisplatin or carboplatin were only to be administered for the first 4 cycles (12 weeks) of therapy.

Note that this includes 19 patients who remained on selpercatinib treatment after initial progression as allowed per protocol, since, in the opinion of the investigator and Sponsor, they were continuing to derive clinical benefit.

Dose intensities

Marked differences were observed in the exposure between the **selpercatinib** and **control arms** in the **Safety-Overall Population**. The median time on treatment was 16.7 months in the **selpercatinib arm** and 9.8 months in the **control arm** (any drug).

Table 8.14 describes dose intensity for the **Safety-Overall Population**. The median relative dose intensities were high in both **selpercatinib** and **control arms** (88.8% and 92.2% to 97.7%, respectively).

Concomitant medication

In the **Safety-Overall Population**, concomitant medications were reported by 99.4% of patients in the **selpercatinib arm** and 100% of patients in the **control arm**. The 2 most frequently used drug classes of concomitant medications as reported in the **selpercatinib arm** (**selpercatinib arm** versus **control arm**) were

- dihydropyridine derivatives (45.2% versus 13.3%), and
- folic acid and derivatives (40.1% versus 78.6%).

Rescue medication

Not applicable.

The Applicant's Position:

The treatment duration and 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 description of treatment compliance, concomitant medications, and rescue medication use. The median duration of treatment in the selpercatinib arm was nearly twice as long as the control arm. This is at least in part due to the ongoing use of selpercatinib until disease progression or unacceptable toxicity, compared to a fixed schedule of chemotherapy/immunotherapy.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Primary Endpoint

At the interim efficacy analysis, LIBRETTO-431 met the primary endpoint (PFS based on RECIST v1.1 according to BICR).

Selpercatinib demonstrated the following results:

- a compelling and statistically significant reduction over 50% in the hazard of disease progression or death
- a clinically meaningful improvement in PFS. The median PFS was over 24 months and more than double the control.
- an early and maintained separation from control in the Kaplan-Meier curves. A separation was observed at the time of the first postbaseline radiographic assessment (6 weeks) (Figure 8.3 and Figure 8.4).
- consistent results across multiple analyses including in:
  - **ITT-Pembrolizumab** and **ITT Populations**
  - all pre-specified subgroups
  - all pre-planned sensitivity analyses, and
  - BICR and investigator assessments.

Table 8.5 summarizes PFS results for the **ITT-Pembrolizumab Population** and Table 8.6 for the **ITT Population** based on BICR.

Table 8.5. Progression-Free Survival by BICR ITT-Pembrolizumab Population Data Cutoff Date: 01 May 2023

	Selpercatinib Arm N = 129 n (%)	**Control Arm N = 83 n (%)**
Number of events, n (%)	49 (38.0)	49 (59.0)
PD	44 (34.1)	46 (55.4)
Death without PD	5 (3.9)	3 (3.6)
Number of patients censored, n (%)	80 (62.0)	34 (41.0)
Median PFS, months (95% CI)	24.84 (16.89, NE)	11.17 (8.77, 16.76)
HR (95% CI), stratified[a]	0.465 (0.309, 0.699)	
p-value, stratified[a,b]	.0002	
PFS rate, % (95% CI)[c]		
6 months	87.2 (80.0, 92.0)	72.1 (60.8, 80.7)
12 months	71.2 (62.0, 78.5)	47.8 (35.9, 58.8)
18 months	58.6 (48.3, 67.5)	34.0 (22.4, 45.9)
24 months	54.2 (43.6, 63.6)	31.6 (20.1, 43.7)
30 months	49.7 (36.6, 61.4)	NE (NE, NE)
Duration of follow-up, median in months (95% CI)	19.38 (16.72, 19.71)	18.86 (14.16, 22.34)

Abbreviations: BICR = blinded independent committee review; CI = confidence internal; HR = hazard ratio; ITT = intent-to-treat; **ITT-Pembrolizumab Population** = patients included in the **ITT population** who were stratified with the intent to receive pembrolizumab in the event of the **control arm** assignment *RET*-altered other cancers; IWRS = integrated web-response system; N = total number of patients in the population; n = number of patients in the specified category; NE = not evaluable; PD = progressive disease; PFS = progression-free survival; *RET* = REarranged during Transfection.

[a] Stratified by IWRS factors geography (East Asian versus non-East Asian) and brain metastases (presence or absence/unknown).

[b] p-value (2-sided) was calculated by the stratified log-rank test.

[c] 95% CIs for the difference between rates were calculated based on normal approximation.

Data cutoff date: 01 May 2023

Table 8.6. Progression-Free Survival by BICR
ITT Population
Data Cutoff Date: 01 May 2023

	Selpercatinib Arm N = 159 n (%)	Control Arm N = 102 n (%)
Number of events, n (%)	61 (38.4)	57 (55.9)
PD	52 (33.7)	54 (52.9)
Death without PD	9 (5.7)	3 (2.9)
Number of patients censored, n (%)	98 (61.6)	45 (44.1)
Median PFS, months (95% CI)	24.84 (17.31, NE)	11.17 (8.77, 16.76)
HR (95% CI), stratified[a]	0.482 (0.331, 0.700)	
p-value, stratified[a,b]	.0001	
PFS rate, % (95% CI)[c]		
6 months	87.0 (80.6, 91.4)	69.8 (59.5, 78.0)
12 months	72.7 (64.6, 79.2)	48.1 (37.2, 58.1)
18 months	58.2 (48.9, 66.4)	34.9 (23.8, 46.3)
24 months	52.2 (42.5, 61.0)	32.6 (21.5, 44.2)
30 months	48.5 (36.9, 59.1)	16.3 (4.0, 36.0)
Duration of follow-up, median in months (95% CI)	19.35 (16.66, 19.58)	16.46 (13.63, 21.03)

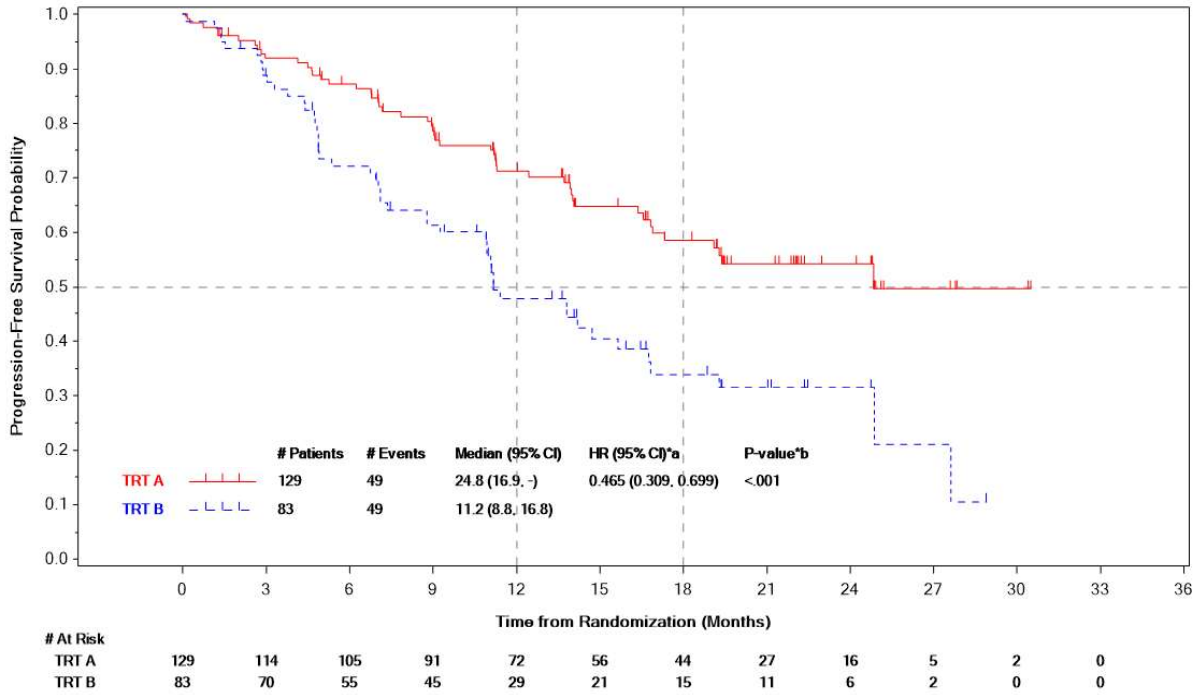
Abbreviations: BICR = blinded independent committee review; CI = confidence internal; HR = hazard ratio; ITT = intent-to-treat; IWRS = integrated web-response system; N = total number of patients in the population; n = number of patients in the specified category; NE = not evaluable; PD = progressive disease; PFS = progression-free survival.

[a] Stratified by IWRS factors geography (East Asian versus non-East Asian) and brain metastases (presence or absence/unknown).

[b] p-value (2-sided) was calculated by the stratified log-rank test.

[c] 95% CIs for the difference between rates were calculated based on normal approximation.

Data cutoff date: 01 May 2023



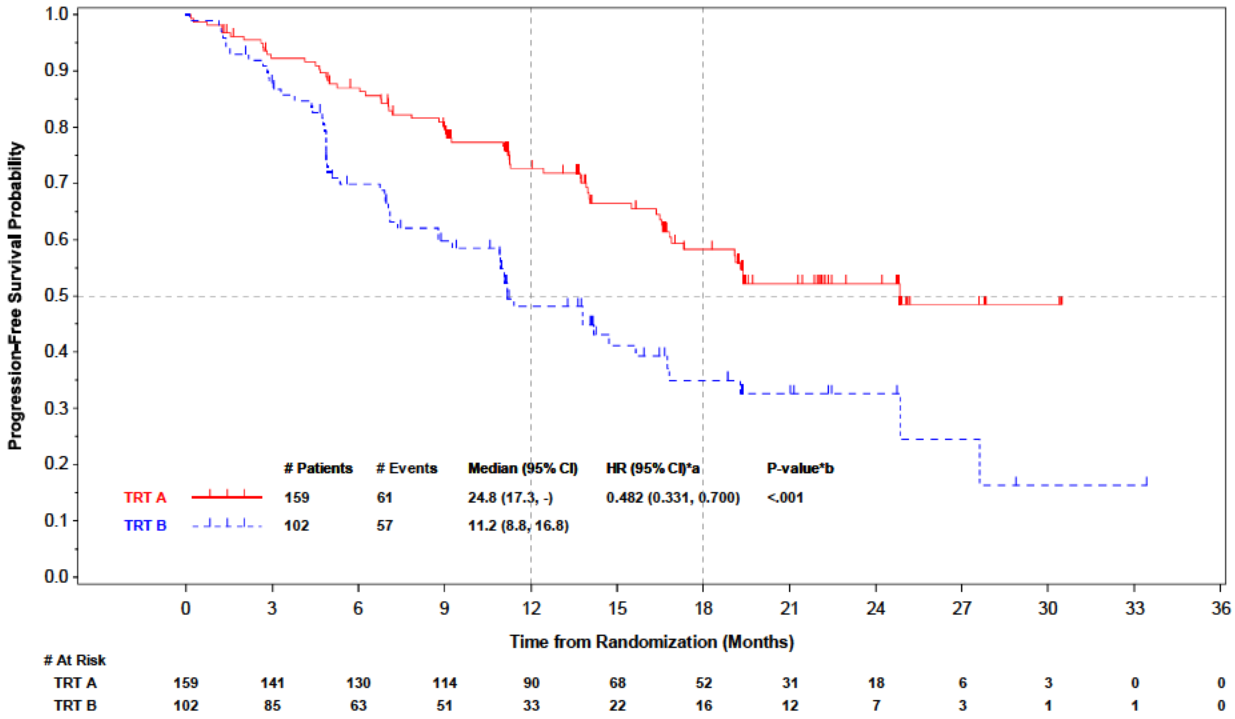
Abbreviations: BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; **ITT-Pembrolizumab Population** = patients included in the **ITT Population** who were stratified with the intent to receive pembrolizumab in the event of the **control arm** assignment; IWRS = integrated web-response system; PFS = progression-free survival; TRT A = selpercatinib; TRT B = carboplatin or cisplatin+pemetrexed+pembrolizumab.

*a HR – IWRS stratified hazard ratio from Cox proportional hazard model and 95% CI of TRT A versus TRT B.

*b Log-rank IWRS stratified p-value (2-sided) for comparison of TRT A versus TRT B.

Data cutoff date: 01 May 2023

Figure 8.3. Kaplan-Meier plot of PFS by BIRC assessment in the ITT-Pembrolizumab Population.



Abbreviations: BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; IWRS = integrated web-response system; PFS = progression-free survival; TRT A = selpercatinib; TRT B = carboplatin or cisplatin+pemetrexed+pembrolizumab.

*a HR - IWRS stratified hazard ratio from Cox proportional hazard model and 95% CI of TRT A versus TRT B.

*b Log-rank IWRS stratified p-value (2-sided) for comparison of TRT A versus TRT B.

Data cutoff date: 01 May 2023

Figure 8.4. Kaplan-Meier plot of PFS by BIRC assessment in the ITT Population.

The Applicant's Position:

The primary endpoint was met in both pre-specified populations, as selpercatinib resulted in a statistically significant improvement in PFS in both the **ITT-Pembrolizumab Population** and **ITT Population**.

The FDA's Assessment:

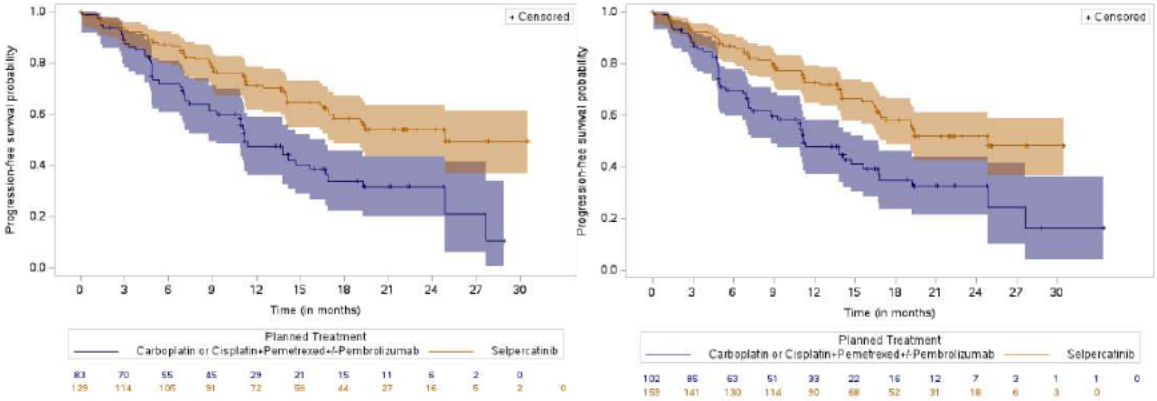
In general, FDA agrees with the Applicant's description of the efficacy results for the primary endpoint of BICR-assessed PFS per RECIST 1.1. Efficacy results are based on the pre-specified interim analysis of PFS at 70% observed IF (planned at 67% IF) in the ITT-Pembro population based on the data cut-off (DCO) date of May 01, 2023. A statistically significant BICR-assessed PFS benefit was observed in the ITT-Pembro population when comparing treatments with selpercatinib vs. investigator's choice of treatments with pembrolizumab and cisplatin or pembrolizumab and carboplatin.

Since BICR-assessed PFS was statistically significant in the ITT-Pembro population, BICR-assessed PFS was then tested hierarchically in the ITT population. A statistically significant PFS benefit was also observed in the ITT population when comparing treatments with selpercatinib vs. investigator's choice of treatments with or without pembrolizumab and cisplatin or carboplatin in the ITT population.

FDA notes that the stratification factors used for the Applicant-provided PFS analysis in the ITT population, presented in the footnote of Table 8.6 above, were geography (East Asian vs. non-East Asian), brain metastases (presence vs. absence/unknown), and Investigator's choice of treatment if randomized to the control arm (with or without pembrolizumab and cisplatin vs. carboplatin) rather than geography (East Asian vs. non-East Asian), brain metastases (presence vs. absence/unknown) only.

The Kaplan-Meier plots of BICR-assessed PFS in the ITT-Pembro population and ITT-Population are presented below (Figure 8.5), and include the 95% confidence interval bands. The PFS curves in the experimental and control arm in both populations appear to separate early and this separation was maintained during the follow-up time.

Figure 8.5. Kaplan-Meier Plots of Progression-Free Survival (PFS) per RECIST 1.1 as Assessed by BICR in ITT-Pembro Population (left) and in ITT Population (right) in Trial LIBRETTO-431



Source: FDA analyses of the Applicant's submitted data (ADTTEIR.xpt)

For the calculation of the primary endpoint of BICR-assessed PFS, patients with no available baseline radiographic tumor assessment or no adequate available post-baseline tumor assessment and death reported after 2 scan intervals following randomization were censored at the time of randomization. Patients who started a new anticancer therapy prior to disease progression were censored at the date of adequate tumor assessment, per RECIST 1.1 criteria, prior to the start of new therapy + 14 days or date of randomization (whichever was later). Patients with radiographic disease progression (PD) by BICR or documented death immediately after 2 or more missing scan intervals following the last adequate tumor assessment or randomization (whichever is later) were censored at the time of last adequate tumor assessment, per RECIST 1.1 criteria, or date of randomization (whichever was later).

Results from the sensitivity analyses of BICR-assessed PFS in the ITT-Pembro population considering (i) death as a PFS event in the event no adequate postbaseline tumor assessment was available and death reported after 2 scan intervals following randomization, (ii) PD or death occurring after the start of a new anticancer therapy as a PFS event, and (iii) PD or death occurring after 2 or more missing scan intervals following last adequate tumor assessment or randomization (whichever was later) as a PFS event appeared to be consistent with the results from the primary analysis of BICR-assessed PFS in the ITT-Pembro population. The sensitivity analyses of the BICR-assessed PFS in the ITT population using the above censoring rules also appeared to be consistent with the results from the primary analysis of PFS in the ITT population.

The randomization ratio was changed from 1:1 (selpercatinib: control) to 2:1 after the start of enrollment in trial LIBRETTO-431. Sensitivity analyses of BICR-assessed PFS using randomization ratio as an additional stratification factor were performed. The results [ITT-

Pembro: PFS HR (95% CI) = 0.46 (0.30, 0.69); ITT: PFS HR (95% CI) = 0.48 (0.33, 0.71)] appear to be consistent with the results observed in the primary analysis.

Subgroup analyses of BICR-assessed PFS in the ITT-Pembro (Table 8.7) and in the ITT population (Table 8.8) are provided below. The efficacy results in the subgroups appear to be consistent with the results observed in their respective overall populations.

Table 8.7. Subgroup Analyses of BICR-assessed PFS in the ITT-Pembro Population

	ITT-Pembro (n=212)	
	# of events/N	**PFS HR (95% CI)**
Age	64/131	0.47 (0.29, 0.77)
<65	34/81	0.52 (0.27, 1.03)
≥ 65		
Sex		
Female	54/113	0.60 (0.35, 1.02)
Male	44/99	0.39 (0.21, 0.70)
Race[1]		
White	43/86	0.57 (0.31, 1.05)
Asian	49/117	0.42 (0.24, 0.73)
American Indian or Alaska Native	2/3	0.71 (0.04, 11.8)
Geography		
East Asian	49/116	0.42 (0.24, 0.74)
Non-East Asian	49/96	0.55 (0.31, 0.98)
Investigator's Intent to Treat With Pembrolizumab	98/212	0.49 (0.33, 0.73)
Brian Metastasis, Baseline		
No	23/71	0.71 (0.30, 1.65)
Yes	27/43	0.51 (0.23, 1.11)
Unknown	48/98	0.40 (0.22, 0.70)
Smoking Status, Baseline		
Former/Never	28/68	0.54 (0.25, 1.13)
Current	70/144	0.48 (0.30, 0.76)

[1] 4 patients had missing race, 2 patients had race reported as Black or African American and both received selpercatinib
BICR, blinded independent central review; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval
Source: FDA analysis of the Applicant's submitted data (ADSL.xpt, ADTTEIR.xpt)

Table 8.8. Subgroup Analyses of BICR-assessed PFS in the ITT-Population

	ITT (n=261)	
	# of events/N	**PFS HR (95% CI)**

Age		
<65	75/157	0.49 (0.31, 0.77)
≥ 65	43/104	0.50 (0.27, 0.92)
Sex		
Female	68/143	0.54 (0.33, 0.87)
Male	50/118	0.43 (0.25, 0.76)
Race[1]		
White	50/101	0.67 (0.38, 1.17)
Asian	59/144	0.43 (0.25, 0.71)
American Indian or Alaska Native	2/3	0.71 (0.04, 11.79)
Geography		
East Asian	58/142	0.44 (0.26, 0.74)
Non-East Asian	60/119	0.57 (0.34, 0.95)
Investigator's Intent to Treat		
With Pembrolizumab	98/212	0.49 (0.33, 0.73)
Without Pembrolizumab	20/49	0.50 (0.19, 1.26)
Brian Metastasis, Baseline		
No	30/95	0.54 (0.26, 1.13)
Yes	29/51	0.48 (0.23, 1.02)
Unknown	59/115	0.49 (0.29, 0.82)
Smoking Status, Baseline		
Former/Never	34/85	0.66 (0.33, 1.31)
Current	84/176	0.42 (0.28, 0.65)

[1] 10 patients had missing race, 2 patients had race reported as Black or African American and both were in selpercatinib arm, 1 patient had race reported as Multiple and was in selpercatinib arm
BICR, blinded independent central review; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval
Source: FDA analysis of the Applicant's submitted data (ADSL.xpt, ADTTEIR.xpt)

FDA considered results from the landmark analyses of PFS presented in this section by the Applicant to be descriptive only.

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 description of data quality and integrity. The data submitted were organized and adequate to perform a complete review of the efficacy of

selpercatinib in patients with treatment-naïve *RET* fusion-positive NSCLC. 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:

Secondary Endpoints

In the **ITT-Pembrolizumab Population**, at the interim efficacy analysis for LIBRETTO-431, improved efficacy was observed with selpercatinib in the secondary endpoints ORR (83.7% [95% CI: 76.2, 89.6] in the **selpercatinib arm** versus 65.1% [95% CI: 53.8, 75.2] in the **control arm** [p=.0028]) and DOR (median DOR was longer in the **selpercatinib arm** than in the **control arm** [24.18 months; 95% CI: 17.94, NE versus 11.47 months; 95% CI: 9.66, 23.26] with an HR of 0.377 [95% CI: 0.224, 0.633; p=.0001]), for patients with *RET* fusion-positive NSCLC compared with control. OS is immature and confounded by a high crossover rate.

The FDA's Assessment:

In general, FDA agrees with the ORR and DOR results per RECIST 1.1 according to BICR as presented in this section. Notably, the ORR in the selpercatinib arm is similar to that observed in the single-arm trial which supported the traditional approval of selpercatinib (refer to Multidisciplinary Review dated May 8, 2020 for details). The ORR of 65% in the control arm suggests that more than half of patients with *RET*-fusion positive NSCLC will have a response to standard of care chemo/immunotherapy, although the duration of this response is shorter than that of selpercatinib.

However, FDA notes that ORR was a secondary endpoint that was not planned to be formally tested. Therefore, FDA considered ORR results descriptive only. In addition, FDA does not agree with the presentation of DOR results with a hazard ratio as the interpretation of such result is challenging in a non-randomized population.

For FDA's assessment regarding OS refer to FDA's comments under "Overall Survival" section below.

Overall Survival

In the **ITT-Pembrolizumab Population**, the HR for OS was 0.961 (95% CI: 0.503, 1.835; p=.9033). In the **ITT Population** an HR of 1.042 (95% CI: 0.578, 1.879; p=.8905) was observed. The OS results at this interim analysis are likely impacted by a high

crossover rate and immaturity of the data in both the **ITT-Pembrolizumab Population** and **ITT Population**.

Crossover rate

Patients randomly assigned to the **control arm** were allowed to crossover to selpercatinib treatment upon confirmation of disease progression by the BICR, if they met the eligibility criteria for crossover.

The on-study crossover rate in the 83 patients randomly assigned to the **control arm** treatment (**ITT-Pembrolizumab Population**) is 43.4%. Since the study is ongoing and many patients are progression free, not all patients are yet eligible to crossover. If only patients that are no longer on control treatment are considered, the on-study crossover is 64.3%.

In addition, selpercatinib and pralsetinib were approved by the FDA and other global regulatory agencies during the conduct of this trial. This provided an opportunity for patients that did not want the additional burden that may come from participating in a clinical trial to receive a commercially available effective selective *RET* inhibitor. A total of 10.7% of patients who are no longer on treatment and did not crossover to on-study selpercatinib received either commercially available pralsetinib or selpercatinib after discontinuing from the control arm treatment. As a result, the effective crossover to a selective *RET* inhibitor was 75%.

Data maturity

The OS results in the **ITT-Pembrolizumab Population** are immature as evidenced by the high censoring rate.

- The censoring rate was 80.6% in the **selpercatinib arm** and 81.9% in the **control arm**.
- Median OS is not yet estimable as over 75% of patients on each arm were still alive at the cutoff date.
- The median follow-up time was 21.65 months in the **selpercatinib arm** and 21.22 months in the **control arm**.
- A total of 40 deaths were observed: 25 of 129 patients in the **selpercatinib arm** and 15 of 83 patients in the **control arm**.

The OS results in the **ITT Population** are also immature.

- An HR of 1.042 (95% CI: 0.578, 1.879; p=.8905) was observed with a median follow-up time of 21.19 months in the **selpercatinib arm** and 20.90 months in the **control arm**.

- The censoring rate was 79.9% in the **selpercatinib arm** and 82.4% in the **control arm**.

The FDA's Assessment:

While, in general, FDA agrees with the presentation of OS results in the ITT-Pembro population in this section, FDA notes that OS in the ITT population was a secondary endpoint in LIBRETTO-431, planned to be formally tested at the time of the interim PFS analysis if BICR-assessed PFS in the ITT population was statistically significant. The final analysis of OS was planned after 175 deaths in the ITT population.

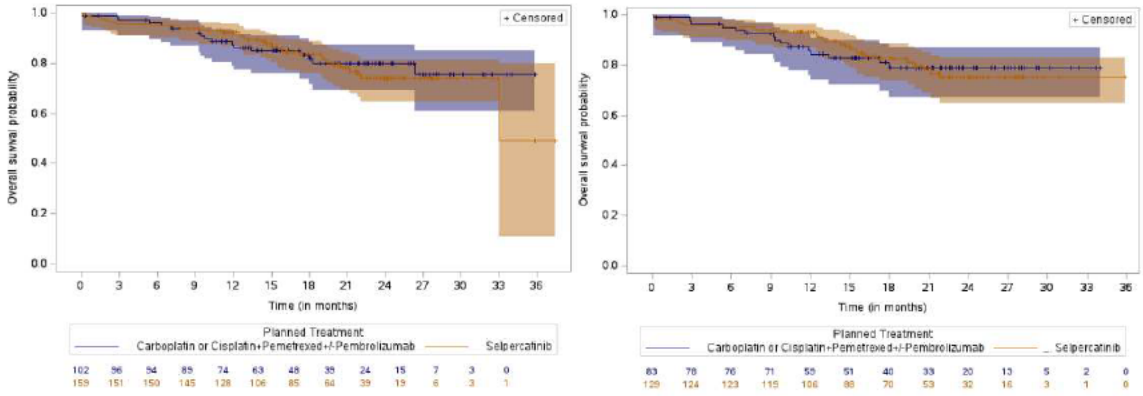
LIBRETTO-431 did not show a statistically significant OS benefit in the ITT population at the time of this interim PFS analysis, with a total of 50 deaths (29% observed IF) observed in this population. OS results in both the ITT population and ITT-Pembro population are presented below (Table 8.9 & Figure 8.6). OS results in the ITT-Pembro population should be considered descriptive only.

Table 8.9. Overall Survival Results in LIBRETTO-431[1]

	ITT (n=261)		ITT-Pembro (n=212)	
Overall Survival (OS)	Selpercatinib N=159	Control N=102	Selpercatinib N=129	Control N=83
Death (%)	32 (20%)	18 (18%)	25 (19%)	15 (18%)
Censored	127 (80%)	84 (82%)	104 (81%)	68 (82%)
Median, months (95% CI)	NR (NE, NE)	33.1 (33.1, NE)	NR (NE, NE)	NR (NE, NE)
Hazard Ratio (95% CI)[2]	1.04 (0.58, 1.88)		0.96 (0.50, 1.84)	
p-value[3]	0.89		Descriptive analysis	

[1]Interim analysis of OS, DCO: 05/01/2023; [2]from stratified Cox regression model; [3]from stratified log-rank test; stratification factors for ITT-Pembro population are geography (East Asian versus non-East Asian) and brain metastases (presence or absence/unknown), and for ITT population are geography (East Asian versus non-East Asian), brain metastases (presence or absence/unknown), and Investigator's choice of treatment if randomized to Arm B (with or without pembrolizumab and cisplatin vs. carboplatin)
Source: FDA analysis of the Applicant's submitted data (ADSL.xpt, ADTTE.xpt).

Figure 8.6. Kaplan-Meier Plots of Overall Survival in ITT (left) and ITT-Pembro (right) Populations in Trial LIBRETTO-431



Source: FDA analysis of the Applicant's submitted data (ADSL.xpt, ADTTE.xpt).

In the ITT population, the Kaplan-Meier curves of OS between the investigational treatment arm and the control arm did not fully separate and had several points of crossing.with overlapping confidence intervals. This result, however, should be interpretated with caution due to immature OS data (27% observed IF) and because 41% (42 out of 102 patients) of patients in the control arm crossed over to the selpercatinib arm.

In the ITT-Pembro population, there were only 40 deaths in the two treatment arms and the crossover rate to the selpercatinib arm was 43% (36 out of 83). The Kaplan-Meier curves of OS between the investigational arm and the control arm in the ITT-Pembro population similarly do not fully separate with several points of crossing and overlapping confidence intervals.

During the review period of this supplemental application, an information request by the FDA was sent to the Applicant to submit an updated descriptive analysis of OS using additional follow-up data. The OS results based on the updated DCO of May 01, 2024, with an additional year of survival follow-up compared to the DCO used for the original

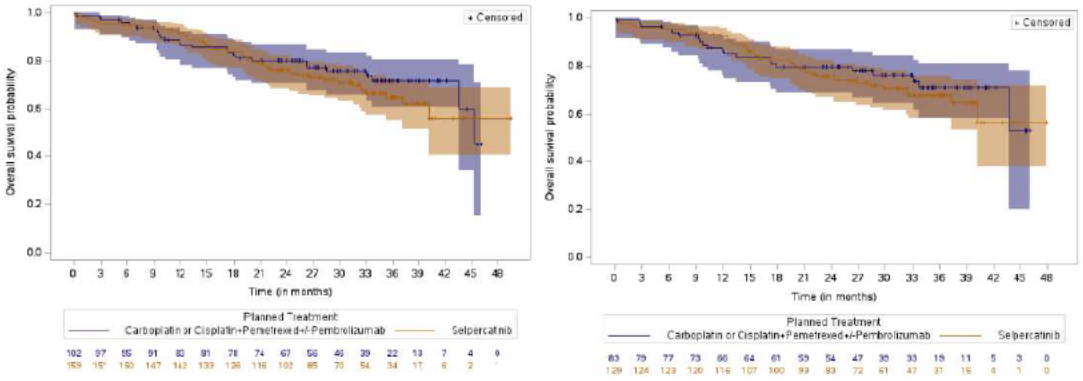
submission (May 01, 2023), are provided below (Table 8.10 & Figure 8.7).

Table 8.10. Overall Survival Results Based on Updated Follow-up in LIBRETTO-431[1]

	ITT (n=261)		ITT-Pembro (n=212)	
Overall Survival (OS)	Selpercatinib N=159	Control N=102	Selpercatinib N=129	Control N=83
Death (%)	49 (31%)	26 (25%)	39 (30%)	21 (25%)
Censored	110 (69%)	76 (74%)	90 (70%)	62 (75%)
Median, months (95% CI)	NE (40.2, NE)	45.3 (43.6, NE)	NE (40.2, NE)	NE (43.6, NE)
Hazard Ratio (95% CI)[2]	1.26 (0.78, 2.04)		1.16 (0.68, 1.98)	

[1]Interim analysis of OS, DCO: 05/01/2024; [2]from stratified Cox regression model; stratification factors for ITT-permbro population are geography (East Asian versus non-East Asian) and brain metastases (presence or absence/unknown), and for ITT population are geography (East Asian versus non-East Asian), brain metastases (presence or absence/unknown), and Investigator's choice of treatment if randomized to Arm B (with or without pembrolizumab and cisplatin vs. carboplatin)
Source: FDA analysis of the Applicant's submitted data (ADSL.xpt, ADTTEOS.xpt).

Figure 8.7. Kaplan-Meier Plots of Overall Survival in ITT (left) and ITT-Pembro (right) Populations in Trial LIBRETTO-431 – Updated Analysis



Source: FDA analysis of the Applicant's submitted data (ADSL.xpt, ADTTEOS.xpt).

In both the ITT-Pembro and ITT populations, the point estimate of OS HR was greater than 1.0. FDA considered several factors that may contribute to the OS results observed in LIBRETTO-431.

Data immaturity

The OS data remain immature at the time of the updated descriptive analysis (43% of prespecified OS events needed for the final analysis). This high proportion of censoring

may introduce uncertainties and result in imprecise estimation of overall survival in this study.

Potential impact of crossover

There was a high rate of crossover in the control arm, with a large proportion of patients going on to receive selpercatinib in the crossover phase of the study or a commercially available RET inhibitor off study. In response to an FDA information request communicated on July 03, 2023, the Applicant provided OS results based on analyses using rank preserving structural failure time model (RPSFTM) among other merhods to adjust for crossover. The RPSFTM is a method that may be used to adjust for treatment switching in trials with survival outcomes. It uses a causal model to predict counter-factual survival times, which are those times that would be observed as if a patient had not crossed over. Using the estimated counter-factual and observed data, RPSFTM attempts to adjust for patient crossover. RPSFTM assumes a common treatment effect, i.e., that the treatment effect of selpercatinib in patients who crossed over from the control arm is same as the treatment effect of selpercatinib in patients who were initially randomly assigned to selpercatinib, and exchangeability of the randomized groups as well as the same survival distribution on average in randomized groups, so that the only difference between randomized groups is the treatment received. According to the Applicant, the OS HR based on RPSFTM was 1.18 and the confidence intervals based on three methods of estimation of causal parameter (log rank, Wald test from Cox or Weibull regression model) ranged from 0.65 to 2.12.

Although results from these analyses may not suggest that the observed overall survival results are strictly due to crossover, they should be interpreted with caution given the immature OS data and the common treatment effect assumption. Additionally, these methods do not take into account the imbalances in post-progression therapies across arms, and rely on treatment effect and exchangeability assumptions required for the methodology.

Potential impact of post-progression therapies

An analysis of post-progression therapies in the ITT population, based on an updated DCO date of May 01, 2024, was submitted to FDA on July 2, 2024, in response to FDA Information request. LIBRETTO-431 allowed crossover after BICR-assessed disease progression; however, BICR-assessed progression was not available at the updated DCO date. Therefore, the receipt of post-progression therapies and corresponding analyses are based on investigator-assessed progression. At the updated DCO date, of the 102 patients randomized to the control arm, 67% (68/102) had investigator-assessed progression, and 64% (65/102) received any post-progression therapy (Table 8.11). Of these 65 patients, 23 patients (35%) received chemotherapy, immunotherapy, or chemo-immunotherapy

treatment, and 64 (98%) received a selective RET inhibitor (selpercatinib or pralsetinib) at any time as a post-progression therapy. Of the 64 who received a selective RET inhibitor, 55 (86%) were patients who crossed over to on-study selpercatinib treatment.

Of the 159 patients randomized to the selpercatinib arm, 45% (71/159) had investigator-assessed disease progression, and 41% (65/159) received any post-progression therapy. Of these 65 patients, 36 patients (55%) received chemotherapy, immunotherapy, or chemo-immunotherapy treatment and 50 patients (77%) received a selective RET inhibitor (selpercatinib or pralsetinib) at any time as a post-progression therapy. Of the 50 patients who received a selective RET inhibitor, 40 patients (80%) continued selpercatinib as on-study treatment beyond progression.

Table 8.11: Summary of Post-Progression Therapies Per Investigator Assessment, ITT population

Summary of Post Progression Therapies per Investigator Assessment — page 1 of 1
ITT Population — 23:00 28JUN2024
J2G-MC-JZJC — PDPM

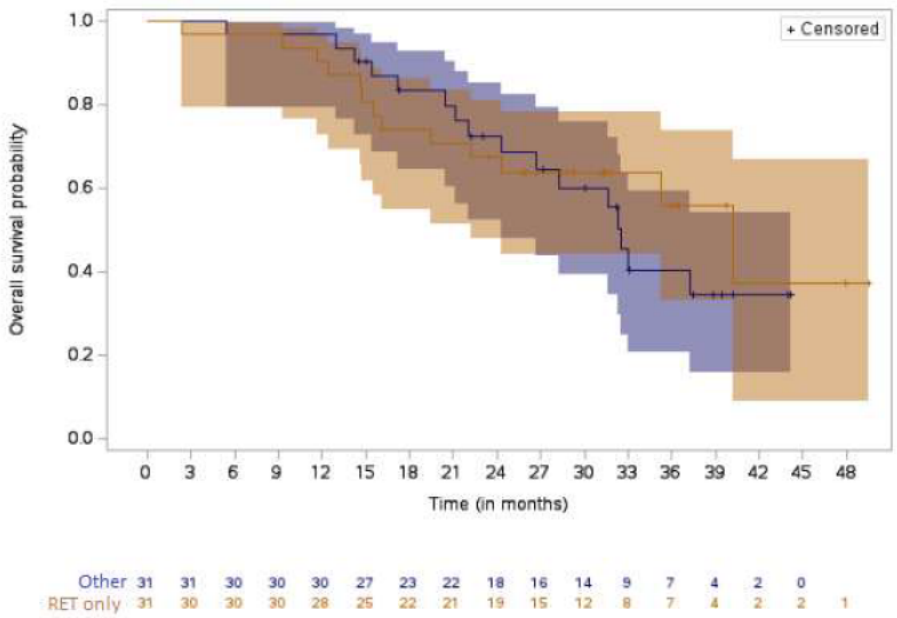
Category	Selpercatinib (N=159) n (%)	Carboplatin or Cisplatin +Pemetrexed+/-Pembrolizumab (N=102) n (%)
Number of patients who received any post progression therapies	65 (40.9)	65 (63.7)
Any Lines		
Number of patients who received selective RET inhibitor	50 (31.4)	64 (62.7)
Number of patients who received chemotherapy	20 (12.6)	11 (10.8)
Number of patients who received immunotherapy	5 (3.1)	1 (1.0)
Number of patients who received chemo-IO	11 (6.9)	11 (10.8)
Number of patients who received other therapies	13 (8.2)	8 (7.8)
Second Line Only		
Number of patients who received selective RET inhibitor	46 (28.9)	55 (53.9)
Number of patients who received chemotherapy	8 (5.0)	1 (1.0)
Number of patients who received immunotherapy	1 (0.6)	0 (0.0)
Number of patients who received chemo-IO	8 (5.0)	9 (8.8)
Number of patients who received other therapies	4 (2.5)	2 (2.0)

Source: Applicant response to FDA IR sent on June 25, 2024

These results indicate that most patients in both arms received selpercatinib at some point during their treatment course. However, only 25% of patients in the selpercatinib arm received chemo-immunotherapy at any point during their treatment course. Therefore, it is possible that treatment with only one effective therapy (i.e., selpercatinib) as opposed to two effective therapies (i.e., selpercatinib and chemo-immunotherapy) may result in worse overall survival. However, the study was not designed to evaluate this question and the data remain immature; therefore, it is challenging to draw definitive conclusions regarding this issue based on the available data.

In an exploratory subgroup analysis restricted to patients from the selpercatinib arm who progressed and received only a selective RET inhibitor as post-progression therapy (n=31) compared to patients who received chemo, immunotherapy, chemo-immunotherapy, and RET inhibitors (n=31) as post-progression therapy resulted in an OS HR (95% CI) of 0.87 (0.42, 1.81). The Kaplan-Meier plot of OS is provided in Figure 8.8.

Figure 8.8: Kaplan-Meier plot of overall survival comparing patients who received RET inhibitor as post progression therapy (n=31) compared to those patients received chemo, IO, Chemo-IO, RET inhibitors (n=31) – selpercatinib arm only



Though the hazard ratio is below 1, the confidence interval is very wide, and the Kaplan-Meier plot indicates crossing curves with overlapping confidence interval bands. No reliable conclusions can be drawn from this subgroup analysis with limited sample size, immature OS data, crossover, and potential non-random selection of patients for post-progression therapies.

Toxicity

FDA compared the safety profiles of the investigational arm compared to the control arm, and while the number of high-grade adverse events and deaths were slightly numerically higher in the selpercatinib arm, in the context of the high crossover rate and fact that most patients on the control arm went on to receive a RET inhibitor post-progression, there

was no clear evidence of worse toxicity that would amount to a detriment in survival for patients receiving selpercatinib (see Section 8.2 for details).

ORR and DOR

Table 8.12 summarizes ORR and DOR for the **ITT-Pembrolizumab Population**.

ORR was higher in the **selpercatinib arm** than in the **control arm**.

Table 8.12. Summary of ORR and DOR by BICR ITT–Pembrolizumab Population Core Study Period

	Selpercatinib Arm N = 129	Control Arm N = 83
Objective response rate (ORR)[a]		
n (%)	108 (83.7)	54 (65.1)
95% CI[b]	(76.2–89.6)	(53.8–75.2)
Stratified odds ratio (95% CI)	2.7 (1.4–5.1)	
Stratified p-value	.0028	
Best overall response, n		
CR	9 (7.0)	5 (6.0)
PR	99 (76.7)	49 (59.0)
SD	14 (10.9)	20 (24.1)
SD16+[c]	7 (5.4)	16 (19.3)
PD	2 (1.6)	5 (6.0)
Not evaluable	5 (3.9)	4 (4.8)
Duration of response		
Responders, n (%)	34 (26.4)	29 (34.9)
Median in months (95% CI)	24.18 (17.94, NE)	11.47 (9.66, 23.26)
Censored, n (%)	74 (57.4)	25 (30.1)
Rate (%) of duration of response[b]		
6 months (95% CI)	92.2 (84.9, 96.0)	77.0 (63.0, 86.2)
12 months (95% CI)	78.8 (69.0, 85.8)	45.7 (30.3, 59.8)
18 months (95% CI)	61.6 (49.9, 71.4)	39.2 (24.0, 54.0)
24 months (95% CI)	59.6 (47.5, 69.8)	22.8 (6.3, 45.5)
Duration of follow-up, median in months	17.97	14.55

Abbreviations: CI = confidence interval; CR = complete response; N = total number of patients in the population; n = number of patients in the specified population; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease; SD16+ = stable disease lasting 16 or more weeks.

a CIs are based on the Clopper-Pearson method.

b 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation

c Time to response is defined as the number of months that elapsed between the date of randomization and the first documentation of objective response (CR or PR, whichever occurred earlier) that was subsequently confirmed.

The FDA's Assessment:

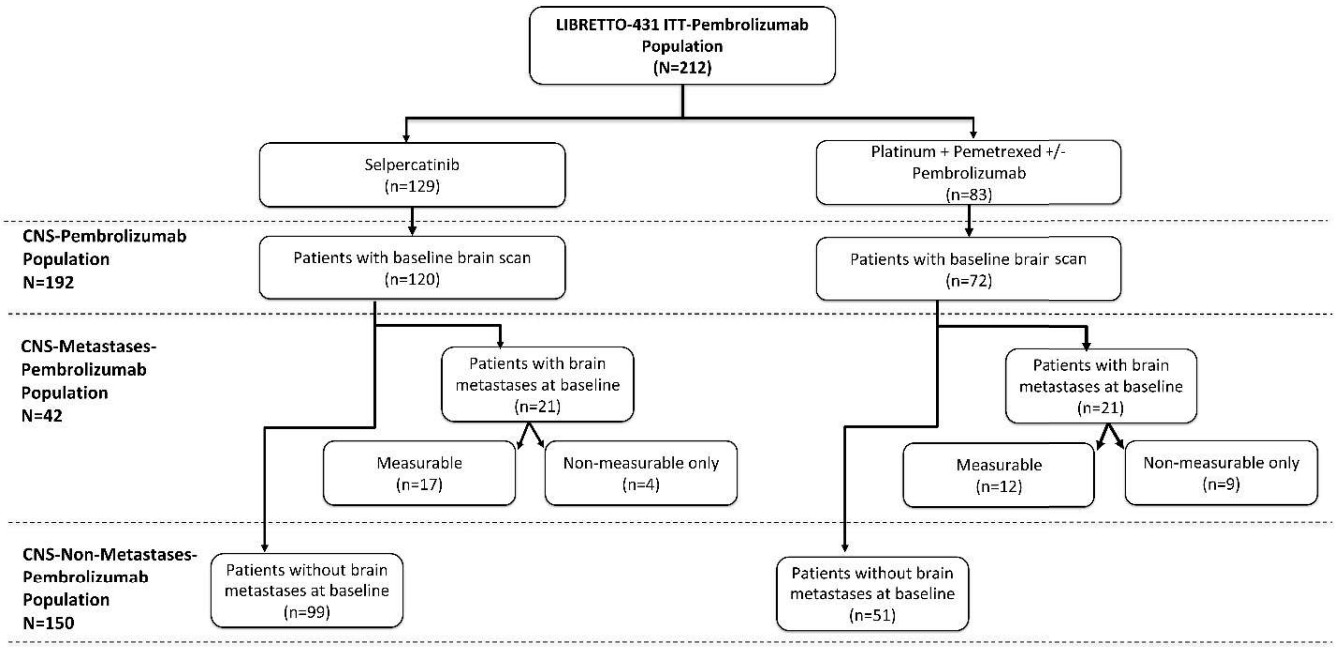
Refer to FDA's comments on ORR and DOR under "Secondary Endpoints" above. FDA also notes that the results under "Duration of response" for the category "Responders, n (%)" are reflective of the number (%) of patients with a DOR event.

CNS Efficacy Analysis

Disposition, Demographics, and Baseline Data for CNS Population

Of the 212 patients in the **ITT-Pembrolizumab Population**, intracranial baseline scans were available for evaluation by neuroradiologic BICR per RECIST 1.1 for 192 patients (**CNS-Pembrolizumab Population**).

Figure 8.9 presents the disposition of patients in the **CNS-Pembrolizumab Population**.



Abbreviations: CNS = central nervous system; **ITT-Pembrolizumab Population** = patients included in the **ITT Population** who were stratified with the intent to receive pembrolizumab in the event of the **control arm** assignment; N = total number of patients in the population; n = number of patients in the specified population.

Figure 8.9. Disposition of patients in the CNS-Pembrolizumab Population.

CNS Efficacy Results

Response outcomes in the CNS-Metastases-Pembrolizumab Population with measurable disease

In patients with measurable brain metastases at baseline, selpercatinib had an improved intracranial ORR and complete response rate when compared with control:

- ORR: 82.4% (95% CI: 56.6, 96.2) in the **selpercatinib arm** versus 58.3% (95% CI: 27.7, 84.8) in the **control arm**
- Complete response rate: 6 of 17 patients (35.3%) in the **selpercatinib arm** versus 2 of 12 patients (16.7%) in the **control arm.**

The median DOR was not reached, as the data are immature. The median follow-up time for DOR was

- 9.92 months (95% CI: 7.66, 18.10) in the **selpercatinib arm**, and
- 12.68 months (95% CI: 2.79, NE) in the **control arm**.

At the 6-month landmark, a greater percentage of patients remained in response:

- **selpercatinib arm:** 92.9% (95% CI: 59.1, 99.0) versus
- **control arm:** 83.3% (95% CI: 27.3, 97.5).

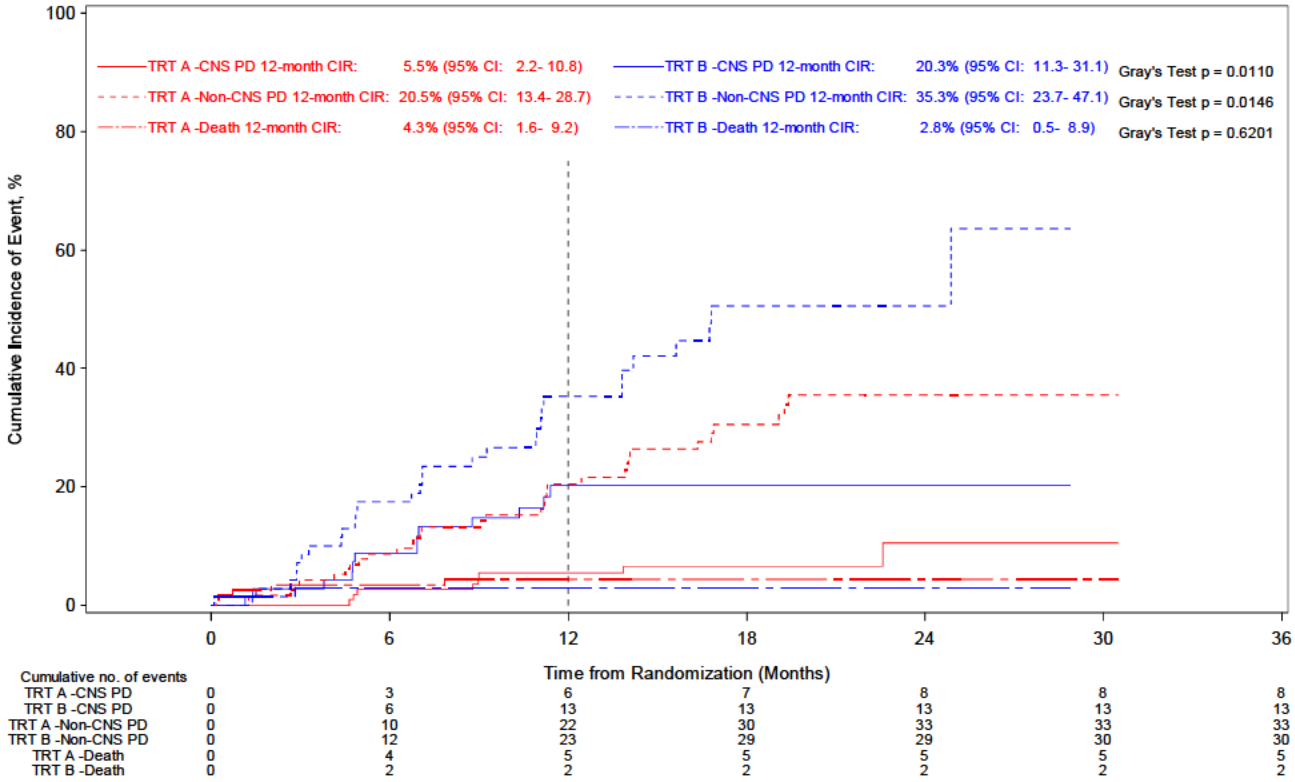
Time to CNS progression in the CNS-Pembrolizumab Population

In the **CNS-Pembrolizumab Population**, the time to cause-specific CNS progression was improved with **selpercatinib** (HR: 0.28; 95% CI: 0.12, 0.68; p=.003), with 8 patients (6.7%) on **selpercatinib** having a first event of CNS progression compared with 13 patients (18.1%) on **control**.

The benefit with **selpercatinib** was observed for patients with (cause-specific HR: 0.61; 95% CI: 0.19, 1.92; p=.391) and without baseline CNS metastases (cause-specific HR: 0.17; 95% CI: 0.04, 0.69; p=.005).

The CIR of CNS progression, with the adjustment for the competing risks of non-CNS progression and death, was lower with **selpercatinib** compared with **control**, with a 12-month CIR of CNS progression (Figure 8.10) of

- 5.5% (95% CI: 2.2, 10.8) in the **selpercatinib arm** versus
- 20.3% (95% CI: 11.3, 31.1) in the **control arm**.



Abbreviations: CI = confidence interval; CIR = cumulative incidence rate; CNS = central nervous system; PD = progressive disease; TRT A = **selpercatinib arm**; TRT B = **control arm**.

Figure 8.10. CIR curves for CNS progression, non-CNS progression, and death in the CNS-Pembrolizumab Population.

Twelve-month CIRs of CNS progression in patients with baseline CNS metastases were

- 25.7% (95% CI: 8.8, 46.7) in the **selpercatinib arm** versus
- 33.3% (95% CI: 14.3, 53.8) in the **control arm.**

Twelve-month CIRs of CNS progression in patients without baseline CNS metastases were

- 1.1% (95% CI: 0.1, 5.2) in the **selpercatinib arm** versus
- 14.7% (95% CI: 5.7, 27.6) in the **control arm**.

The Applicant's Position:

The results for the ORR and DOR in the **ITT Population** were consistent with those observed in the **ITT-Pembrolizumab Population**. The results in the **CNS-Overall**

Population were consistent with those observed in the **CNS-Pembrolizumab Population**.

Overall response rate by RECIST 1.1 was higher and responses were more durable with selpercatinib. OS is immature and confounded by crossover. In patients with measurable CNS disease at baseline, selpercatinib demonstrated improved outcomes in intracranial response rate by RECIST 1.1 including complete responses, and modified DOR. (b) (4) (b) (4) (b) (4)

The FDA's Assessment:

FDA agrees with the Applicant's position that intracranial ORR and DOR per RECIST 1.1 by BICR were secondary endpoints in the LIBRETTO-431 trial. Of the 212 patients in the ITT-Pembro population, 29 patients (14%) had measurable intracranial metastases at baseline, as determined by a neuroradiologic BIRC. Responses in intracranial lesions were observed in 14 of 17 patients treated with selpercatinib and 7 of 12 patients treated with chemotherapy with pembrolizumab.

FDA does not agree with the statement, (b) (4) (b) (4) (b) (4) It is challenging to draw conclusions about the (b) (4) (b) (4) based on these data.

Dose/Dose Response

Data:

Refer to Section 6.2.2.1.

The Applicant's Position:

For the *RET* fusion-positive NSCLC indication, the Sponsor continues to recommend a weight-based dosing regimen of selpercatinib (120 mg for patients weighing less than 50 kg and 160 mg for those weighing 50 kg or greater).

The FDA's Assessment:

FDA agrees with the Applicant's position regarding weight-based dosing for patients who are 12 years and older. Refer to Section 6 for additional details.

Durability of Response

Data:

Refer to the data in Table 8.12.

The Applicant's Position:

Refer to the efficacy results in Section 8.1.2.

The FDA's Assessment:

Refer to FDA's comments on duration of response under "Secondary Endpoints" in Section 8.1.

Persistence of Effect

Data:

Refer to the data in Table 8.12.

The Applicant's Position:

Although long-term controlled studies specifically designed to collect long-term efficacy data have not been conducted, (b) (4)

(b) (4)

The FDA's Assessment:

Not applicable

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

In the **ITT-Pembrolizumab Population**

- the median time to confirmed deterioration (TTCD) of pulmonary symptoms, defined by time from the date of randomization to the date of the first 2-point or more increase of the Non-Small Cell Lung Cancer Symptom Assessment Questionnaire total score and confirmed at the next subsequent assessment, was not reached for the **selpercatinib arm** versus 1.9 months (95% CI: 0.7, 6.6) for the **control arm** (HR: 0.34 [95% CI: 0.20, 0.55; p<.001]), and

- median TTCD of physical function, defined by time from the date of randomization to the date of the first 5-point or more decrease of EORTC QLQ-C30 Physical Functioning score and confirmed at the next subsequent assessment, was 2.8 months (95% CI: 1.3, 5.6) for the **selpercatinib arm** versus 0.5 month (95% CI: 0.4, 1.2) in the **control arm** (HR: 0.54 [95% CI: 0.38, 0.76; p<.001]).

The Applicant's Position:

In the **ITT-Pembrolizumab Population**, there were 23.3% of patients in the **selpercatinib arm** who had confirmed deterioration of patient-reported pulmonary symptoms compared to 43.4% in the **control arm**. The PRO data on physical function also showed that 58.9% in the **selpercatinib arm** had confirmed deterioration compared to 68.7% in the **control arm**. A longitudinal analysis showed that overall quality of life, measured by the EORTC QLQ-C30 Global Health Status/quality of life scale, was maintained over time, compared to baseline, for both arms. Patients tolerated both treatments well, as measured by the Functional Assessment of Cancer Therapy-General Item GP5 (bothered [score 2, 3, or 4], with 23.6% in the **selpercatinib arm** versus 38.1% in the **control arm** in a longitudinal analysis up to 52 week on-treatment period. PRO results were consistent in the **ITT Population**. (b) (4) (b) (4)

The FDA's Assessment:

FDA agrees with the Applicant's position that time to deterioration in pulmonary symptoms as measured by the NSCLC-SAQ was a secondary endpoint in the LIBRETTO-431 trial for descriptive only. This endpoint was not included in the statistical analysis plan for formal testing and thresholds for meaningful change were not agreed upon with FDA prior to study analyses.

The time to confirmed deterioration (TTCD) of pulmonary symptoms and TTCD of physical function endpoints are difficult to interpret due to multiple considerations, including variable baseline lung functioning, fluctuations in lung functioning due to the underlying disease, other intercurrent events, concomitant medications, reversibility of the deterioration event, and missing data. At least 30% of patients in both arms had no PRO data completed or no baseline PRO data. It is unclear whether a 2-point or more increase of the Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ) total score, or a 5-point or more decrease of EORTC QLQ-C30 Physical Functioning score is clinically meaningful. These thresholds lack sufficient justification and were not discussed with FDA. In addition, the completion rates for NSCLC-SAQ, EORTC QlQ-C30 and FACT-GP5 were not clearly reported. FDA considers these analyses of patient-reported outcome (PRO) endpoints to be exploratory in nature and did

not independently verify the results. (b) (4)
(b) (4)

Additional Analyses Conducted on the Individual Trial

Data:

Not provided in this submission.

The FDA's Assessment:

Not applicable

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

The Applicant previously provided substantial evidence of effectiveness of selpercatinib 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, as described in the multidisciplinary review dated September 21, 2022 (sNDA 213246 Supplement 7). The traditional approval was based on objective response rate (ORR) and duration of response (DOR) data, with substantial durability of responses in additional patients supported by consistent ORR results, in both treatment-naïve and previously treated patients with *RET* fusion-positive NSCLC enrolled in Study LOXO-RET-17001 (LIBRETTO-001), an international, single-arm, dose-escalation and multi-cohort expansion study that supported the accelerated approval of selpercatinib. FDA did not require a randomized controlled trial to verify the benefit of selpercatinib for this indication due to the perceived lack of equipoise with high overall response rates with prolonged durations of response in a rare biomarker driven population. However, a randomized trial was conducted by the Applicant and submitted to FDA in this supplemental application with a request to update product labeling with new efficacy results for the existing indication.

The efficacy evaluation for this sNDA is based primarily on the results of Study LIBRETTO-431, a multi-regional, open-label, randomized, active-controlled trial of selpercatinib versus platinum-based and pemetrexed chemotherapy with or without pembrolizumab in patients with treatment-naïve *RET* fusion-positive, unresectable locally advanced or metastatic NSCLC.

The primary efficacy population included 212 patients enrolled in LIBRETTO-431 with an intent to treat with pembrolizumab if randomized to the control arm (129 into selpercatinib arm and 83 into chemotherapy with pembrolizumab arm). A 13.6-month improvement in progression-free survival (PFS) as determined by a blinded independent review committee (BIRC) according to RECIST v1.1, the major efficacy outcome measure, was observed at the first planned interim analysis (median PFS: 24.8 months in selpercatinib arm vs. 11.2 months in control arm), with a hazard ratio (HR) of 0.47 (95% Confidence Interval [CI] 0.31, 0.70).

Overall survival (OS) was immature at the time of the PFS interim analysis. At the time of an updated descriptive analysis of OS (43% of prespecified OS events needed for the final analysis), a total of 49 (31%) and 26 (25%) patients died in the selpercatinib and the control arm, respectively. The OS HR was 1.26 (95% CI: 0.78, 2.04). These results are not reliable due to the immaturity of the data. Further, overall survival may be affected by the imbalance in post-progression therapies. Per the most recent DCO, of 68 patients on the control arm who had disease progression, 50 patients (74%) received selpercatinib at first progression. Of 71 patients on the selpercatinib arm who had disease progression, 16 (23%) received chemotherapy and/or immune checkpoint inhibitor therapy, and 44 (62%) continued receiving selpercatinib at the time of first progression.

The review team considers the benefits of selpercatinib to outweigh the risks in the intended population even though the point estimate of the OS HR is greater than 1.0 at the most recent analysis. These considerations include the prior determination of substantial evidence of effectiveness based on a high ORR with substantial DOR in a single adequate and well-controlled trial (LIBRETTO-001). Subsequent study in a second adequate and well-controlled trial, LIBRETTO-431, has confirmed these results, demonstrating an ORR >80% with DOR >20 months in both studies. The results of LIBRETTO-431 also demonstrate a >1 year improvement in PFS compared to chemo-immunotherapy, with a HR of 0.47 (95% CI: 0.31, 0.70) and without evidence of deaths due to toxicity, which the review team considers to be clinically meaningful. The study design of LIBRETTO-431 impacted the interpretability of the overall survival results, primarily that crossover was permitted and the majority of patients on the control arm went on to receive selpercatinib in the crossover phase of the study or alternatively, a commercially available RET inhibitor off study. In addition, most patients in the selpercatinib arm did not receive standard of care chemo-immunotherapy at any point during their treatment course. Therefore, it is possible that treatment with only one effective therapy (i.e., selpercatinib) as opposed to two effective therapies (i.e., selpercatinib plus chemo-immunotherapy) may impact overall survival. However, the study was not designed to evaluate this question and the data remain immature; therefore, it is challenging to draw definitive conclusions regarding this issue based on the available data. Finally, while the safety profiles of selpercatinib vs. chemo-immunotherapy differed, there was no clear evidence that worse toxicity would result in differential overall survival for patients receiving selpercatinib.

The FDA Guidance for Industry entitled, "Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format," states that the Clinical Studies section of product labeling must discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively (21 CFR 201.57(c)(15)). Generally, this should include information from the adequate and well-controlled studies that demonstrate the effectiveness of the drug for its approved indication. This section of the labeling is not intended to describe all available effectiveness data. However, clinical studies that prospectively evaluate an important safety endpoint, as well as clinical studies that provide other important information about a drug's effectiveness not furnished by the studies that provide primary support for effectiveness, should usually be included in the Clinical Studies section. Examples provided in the guidance include the following:

- Studies that suggest differential effects in population subsets (e.g., women vs. men, presence or absence of concomitant illness or medications)
- Studies that suggest lack of effectiveness in a clinical situation or lack of effect on a particular endpoint where the drug might have been expected to work
- Studies that provide information relevant to dose selection or adjustment (e.g., dose-response studies or studies in nonresponders to a particular dose)
- Studies that provide information about the nature and size of the treatment effect, particularly where the effect is small

The results of study LIBRETTO-431 provide information about the effectiveness of selpercatinib not furnished by the studies that provided primary support for effectiveness. Specifically, these data provide additional information about the nature and size of the treatment effect of selpercatinib in patients with treatment-naïve *RET* fusion-positive NSCLC, as well as randomized safety data which complement the existing safety database from single arm trials. Therefore, the review team recommends inclusion of the results of Study LIBRETTO-431 in the product labeling for selpercatinib. A post-marketing commitment will be included in the approval letter to obtain final OS results from LIBRETTO-431.

8.1.4. Assessment of Efficacy Across Trials

Primary Endpoints

Data:

Not provided in this submission.

The FDA's Assessment:

Not applicable

Secondary and Other Endpoints

Data:

Not provided in this submission.

The FDA's Assessment:

Not applicable

Subpopulations

Data:

Not provided in this submission.

The FDA's Assessment:

Not applicable

Additional Efficacy Considerations

The FDA's Assessment:

Not applicable

8.1.5. Integrated Assessment of Effectiveness

Data:

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.

8.2. Review of Safety

Data:

Not applicable.

The Applicant's Position:

The safety analyses from the **Safety-Overall Population** provide the primary basis for the safety profile of selpercatinib in patients with *RET* fusion-positive NSCLC.

Overall, the safety findings in the **Safety-Overall Population** and the **Safety-Pembrolizumab Population** were similar unless specifically stated. No clinically meaningful difference in the safety profile between the **Safety-Overall Population** and the **Safety-Pembrolizumab Population** was observed.

The FDA's Assessment:

FDA agrees that the analyses from the LIBRETTO-431 overall safety population (N=158), as described in the sections below, provided the primary basis for the safety profile of selpercatinib in patients with treatment-naïve *RET* fusion-positive NSCLC. These data were supported by the broader population of 796 patients with *RET* fusion-positive advanced solid tumors who received selpercatinib in single-arm study LIBRETTO-001.

8.2.1. Safety Review Approach

Data:

Not applicable.

The Applicant's Position:

The safety profile of selpercatinib is characterized by toxicities that are manageable through routine monitoring, dose modifications, and standard clinical management for patients with advanced cancer. Relative to control, an increase in the overall frequency of AEs including TEAEs, SAEs, AESIs, and permanent discontinuations due to TEAEs was reported in patients treated with selpercatinib in LIBRETTO-431. Specific dose modification recommendations for the ADRs of ALT/AST increased, hypersensitivity, hypertension, and QT prolongation allow the majority of patients who experience these events to continue on selpercatinib treatment.

AEs reported through postmarketing sources continue to be monitored through routine pharmacovigilance.

No new or additional risk minimization or pharmacovigilance activities were warranted for the newly determined ADRs and thus, there was no impact to the benefit-risk profile of selpercatinib. Selpercatinib continues to be well managed, with key toxicities that are easily identifiable, mostly low grade, and manageable with few discontinuations due to AEs.

The FDA's Assessment:

FDA agrees that the safety profile of selpercatinib observed in the LIBRETTO-431 overall safety population (N=158) is reflective of the known safety profile of selpercatinib in other approved indications and across other clinical studies.

The safety population used to inform the Warnings and Precautions section (Section 5) 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) and were enrolled prior to the data cut-off date of June 15, 2021.

The safety data from LIBRETTO-431 were included in the Adverse Reactions section (Section 6) of the product labeling, with a data cut-off of May 1, 2023.

The safety results are viewed in the setting of the existing clinical experience with the product and its post-marketing safety database.

8.2.2. Review of the Safety Database

The evaluation will focus on the safety profile observed in the LIBRETTO-431 **Safety-Overall Population**.

Unless noted, the safety findings in the **Safety-Pembrolizumab Population** were consistent with those in the Safety-Overall Population.

Overall Exposure

Data:

The median time on treatment was 16.7 months in the **selpercatinib arm** and 9.8 months in the **control arm** (any drug) as presented in Table 8.13.

Per protocol, cisplatin or carboplatin were only to be administered for the first 4 cycles (12 weeks) of therapy.

Table 8.13. Summary of Exposure and Dose Intensity LIBRETTO-431 Safety-Overall Population

	Selpercatinib Arm N = 158	Control Arm N = 98				
	Selpercatinib	Cisplatin	Carboplatin	Pemetrexed	Pembrolizumab	Any Drug
Relative dose intensity, median	88.8	93.5	94.1	92.2	97.7	NA
Median duration of treatment, months	16.7	2.8	2.8	7.0	10.0	9.8
Median number of cycles received per patient	20	4	4	10	13.5	13

Abbreviations: N = number of patients in the analysis population; NA = not applicable.

The Applicant's Position:

Relative dose intensity was high and similar across the two treatment arms which provides evidence of selpercatinib's acceptable tolerability.

The FDA's Assessment:

FDA agrees with the Applicant's position that the median relative dose intensity was high across both treatment arms. The median time on treatment was approximately 7 months longer in the selpercatinib arm compared to the control arm, which is expected given the continuous administration of selpercatinib (until progressive disease or unacceptable toxicity) compared to the fixed dosing regimens of chemo-immunotherapy.

Relevant characteristics of the safety population:

Data:

Overall baseline demographic and disease characteristics were similar across populations and well balanced between the treatment arms, with the exception of race or region.

The Applicant's Position:

The safety profile of selpercatinib was consistent and well tolerated across populations except for patients from the East Asian region, where a higher frequency of specific AEs was observed. East Asian patients in the selpercatinib arm had an increased incidence of TEAEs, including liver

events, hematological events, increased creatinine, hypertension, and QT prolongation, compared with non-East Asian patients.

The FDA's Assessment:

FDA agrees with the Applicant's position that the demographic characteristics were generally similar between the two treatment arms (Table 8.14). Refer to Section 8.2.7 for a review of safety analyses by demographic subgroup.

Table 8.14: Demographics Summary: Overall Safety Population

Demographic Parameter		Selpercatinib (N=158)	Carboplatin or Cisplatin +Pemetrexed +/-Pembrolizumab (N=98)	Total (N=256)
Sex n(%)	n	158	98	256
	Female	85 (53.8)	54 (55.1)	139 (54.3)
	Male	73 (46.2)	44 (44.9)	117 (45.7)
Age (yrs)	n	158	98	256
	Mean (SD)	60.3 (11.2)	60.6 (11.5)	60.4 (11.3)
	Median	61.0	62.0	62.0
	Min - Max	31 - 87	31 - 83	31 - 87
Age categories n(%)	n	158	98	256
	<65	99 (62.7)	56 (57.1)	155 (60.5)
	>=65	59 (37.3)	42 (42.9)	101 (39.5)
Race n(%)	n	154	92	246
	American Indian or Alaska Native	2 (1.3)	1 (1.1)	3 (1.2)
	Asian	92 (59.7)	50 (54.3)	142 (57.7)
	Black or African American	2 (1.3)	0	2 (0.8)
	Native Hawaiian or Other Pacific Islander	0	0	0
	White	57 (37.0)	41 (44.6)	98 (39.8)
	Multiple	1 (0.6)	0	1 (0.4)
	Missing	4	6	10
Ethnicity n(%)	n	7	9	16
	Hispanic or Latino	0	0	0
	Not Hispanic or Latino	7 (100.0)	8 (88.9)	15 (93.8)
	Not reported	0	1 (11.1)	1 (6.3)
	Missing	151	89	240
Weight (kg)	n	158	98	256
	Mean (SD)	66.3 (14.7)	67.8 (14.5)	66.8 (14.6)
	Median	64.2	66.4	65.0
	Min - Max	42 - 136	42 - 115	42 - 136
Height (cm)	n	156	98	254
	Mean (SD)	164.2 (9.6)	164.8 (9.1)	164.4 (9.4)
	Median	163.5	165.0	164.0
	Min - Max	145 - 184	146 - 185	145 - 185
BMI (kg/m^2)	n	156	98	254
	Mean (SD)	24.52 (4.54)	24.81 (4.20)	24.63 (4.40)
	Median	23.62	24.33	24.09
	Min - Max	16.4 - 43.7	17.5 - 38.6	16.4 - 43.7
Country n(%)	n	158	98	256
	Argentina	2 (1.3)	0	2 (0.8)
	Australia	2 (1.3)	2 (2.0)	4 (1.6)
	Belgium	3 (1.9)	3 (3.1)	6 (2.3)
	Brazil	7 (4.4)	1 (1.0)	8 (3.1)
	Canada	2 (1.3)	1 (1.0)	3 (1.2)
	China	62 (39.2)	28 (28.6)	90 (35.2)
	Czech Republic	0	1 (1.0)	1 (0.4)
	France	2 (1.3)	4 (4.1)	6 (2.3)

Country n(%)	Germany	5 (3.2)	4 (4.1)	9 (3.5)
	Greece	2 (1.3)	0	2 (0.8)
	Hong Kong	4 (2.5)	1 (1.0)	5 (2.0)
	Israel	1 (0.6)	4 (4.1)	5 (2.0)
	Italy	19 (12.0)	11 (11.2)	30 (11.7)
	Japan	15 (9.5)	10 (10.2)	25 (9.8)
	Korea, Republic of	8 (5.1)	6 (6.1)	14 (5.5)
	Mexico	4 (2.5)	1 (1.0)	5 (2.0)
	Netherlands	2 (1.3)	1 (1.0)	3 (1.2)
	Poland	0	1 (1.0)	1 (0.4)
	Russian Federation	1 (0.6)	2 (2.0)	3 (1.2)
	Spain	7 (4.4)	9 (9.2)	16 (6.3)
	Taiwan	2 (1.3)	4 (4.1)	6 (2.3)
	Turkey	8 (5.1)	0	8 (3.1)
	Ukraine	0	4 (4.1)	4 (1.6)
Region n(%)	n	158	98	256
	East Asia	91 (57.6)	49 (50.0)	140 (54.7)
	Non-East Asia	67 (42.4)	49 (50.0)	116 (45.3)

Cutoff Date: 2023-05-01.
Abbreviations: N = number of subjects in analysis population; n = number of subjects;
SD = Standard Deviation; Min = Minimum; Max = Maximum
Note: number of subjects with non-missing data, used as denominator.

Source: LIBRETTO-431 CSR, Table JCJC.8.7, pages 181-183)

Adequacy of the safety database:

Data:

Table 8.15 describes the safety analysis sets included in LIBRETTO-431. All safety analyses are performed for the core study period.

Table 8.15. Description of Safety Analysis Sets to Be Included in the sNDA LIBRETTO-431 Data Cutoff Date: 01 May 2023

Safety Analysis	Analysis Set Description
Safety-Overall (N = 256) Selpercatinib (N = 158) Control (N = 98)	All randomly assigned patients who took at least 1 dose (including a partial dose) of the study treatment. Analysis of safety data will be based on the actual treatment a patient received on the first study treatment administration regardless of which treatment they were randomized to receive ("as treated").
Safety-Pembrolizumab (N = 209) Selpercatinib (N = 129) Control (N = 80)	Randomly assigned patients stratified to investigator's intent to treat with pembrolizumab and who took at least 1 dose (including a partial dose) of selpercatinib; and all randomized patients who took at least 1 dose (including a partial dose) of pembrolizumab. Analysis of safety data is based on the actual treatment a patient received on the first study treatment administration regardless of which treatment they were randomized to receive ("as treated").

Abbreviations: N = number of patients in the analysis population; sNDA = supplemental new drug application.

The Applicant's Position:

As of the data cutoff of 01 May 2023, more than 1800 patients had received selpercatinib treatment across the development program, including 256 first line patients with NSCLC in LIBRETTO-431. The size of the safety database for selpercatinib is sufficient to adequately characterize the safety profile. LIBRETTO-431 was well designed, with appropriate endpoints, and a robust safety review process.

The FDA's Assessment:

FDA agrees with the Applicant's position that the safety population studied in LIBRETTO-431 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.

8.2.3. 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. Analysis-ready, efficacy, and safety datasets, which support the efficacy and safety of selpercatinib for LIBRETTO-431, are provided.

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

Categorization of Adverse Events

Data:

Evaluation of AEs

All patients who received at least 1 dose of the study drug were evaluated for safety.

Mapping of AEs

Each National Cancer Institute-CTCAE v5.0 term reported by the investigator was mapped to the MedDRA Version 26.0 PT and system organ class of the corresponding MedDRA lower level term, unless the reported CTCAE term was "Other - specify". If the reported CTCAE term was "Other - specify", the MedDRA lower level term, PT, and system organ class mapped from the verbatim AE term were used. All listings and summaries used the PT resulting from this process.

Composite terms

TEAEs are summarized by PT and composite terms, including AESIs. 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 AESIs. All analyses evaluated for AESIs were for treatment-emergent events. Based upon the safety trends observed during the conduct of the ongoing Study LIBRETTO-001, the following event categories are deemed as AESIs:

- Liver injury
- Hypertension
- Drug hypersensitivity, and
- ECG QT prolonged.

AST increased, ALT increased, Hypertension, Hypersensitivity, and ECG QT prolonged are recognized ADRs for selpercatinib.

The AESIs observed with selpercatinib treatment are monitorable and manageable with dose-modification strategies that allow most patients who experience these events to continue therapy.

Other notable events

Other notable events include the AEs within the Warnings and Precautions section of the USPI that are not included in the AESI:

- Hemorrhagic events
- Tumor lysis syndrome
- Risk of impaired wound healing
- Embryo-fetal toxicity
- Interstitial lung disease/pneumonitis, and
- Hypothyroidism.

The Applicant's Position:

All data were collected and assessed appropriately to allow thorough analyses of AEs.

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

Routine Clinical Tests

Data:

Routine hematology, coagulation, urinalysis, pregnancy, ECG, and vital signs assessments were performed locally. Chemistry laboratory tests were performed locally and/or centrally. Hepatic monitoring and thyroid tests were performed centrally.

The Applicant's Position:

Assessments performed were appropriate.

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

8.2.4. Safety Results

Deaths

Data:

Table 8.16 presents a summary of deaths in the **Safety-Overall Population**.

Deaths in the core study period

Overall, a higher percentage of deaths occurred in the **selpercatinib arm** compared with the **control arm**: 32 deaths (20.3%) vs 17 deaths (17.3%).

Table 8.16. Summary of Deaths
LIBRETTO-431
Safety-Overall Population

	LIBRETTO-431 Safety-Overall Population N = 256	
	Selpercatinib Arm (N = 158) n (%)	**Control Arm (N = 98) n (%)**
All deaths	**32 (20.3)**	**17 (17.3)**
Deaths on therapy or within 30 days of discontinuation of study therapy	**10 (6.3)**	**2 (2.0)**
Adverse events	7 (4.4)	0
AEs related to study treatment	2[a] (1.3)	0
Study disease	3 (1.9)	2 (2.0)
Deaths after 30 days of discontinuation of study therapy[b]	**22 (13.9)**	**15 (15.3)**
Adverse events	0	1 (1.0)
AEs related to study treatment	0	1 (1.0)
Study disease	20 (12.7)	14 (14.3)
Death	2[c] (1.3)	0

Abbreviations: AE = adverse event; N = number of patients in the analysis population; n = number of patients in the specified category.

a Deaths due to AEs related to the study treatment (by investigator assessment) included sudden death and malnutrition.

b For the **control arm**, these events may have occurred on crossover treatment. Specifically, the death due to an AE was a patient in the crossover period who died due to respiratory failure while on selpercatinib treatment and deemed by the investigator to be related to selpercatinib.

c Two deaths due to unreported causes occurred after 37 and 450 days, respectively, after selpercatinib discontinuation.

Note: Percentage is calculated based on the number of patients in the column heading as the denominator.
Data cutoff date: 01 May 2023

The Applicant's Position:

The majority of deaths observed in the **selpercatinib arm** were due to progressive disease. The incidence of deaths due to AEs observed in the **selpercatinib arm** was consistent with those observed previously in the selpercatinib development program.

TEAEs leading to death in the selpercatinib arm during core study period

In the core study period, 7 (4.4%) of the 158 patients had TEAEs with a fatal outcome in the **selpercatinib arm**, which occurred on therapy or within 30 days of discontinuation of study therapy:

- 6 deaths occurred due to an AE while on study treatment
  - 2 deaths occurred due to myocardial infarction, and
  - 1 death each occurred due to acute respiratory failure, cardiac arrest, malnutrition, and sudden death, and
- 1 death occurred due to respiratory failure within 30 days of treatment discontinuation.

TEAEs leading to death in the selpercatinib arm during crossover study period

In the crossover period, 10 patients died due to progressive disease after 30 days of discontinuation of the **control arm** treatment.

Additionally, 1 death due to an AE more than 30 days after drug discontinuation was reported for the **control arm**. However, this event occurred during the crossover period when the patient was on selpercatinib treatment, and the fatal event of respiratory failure was deemed related to selpercatinib by the investigator.

Summary of fatal AEs

Based on the review of the individual fatal events, no clear pattern that would suggest a common pathophysiology associated with selpercatinib could be identified. Tumor involvement and progressive disease could not be ruled out as contributing factors in 50% (4 of 8) of the fatal events in patients receiving selpercatinib. No clear pattern in time to onset was observed, where the time to event onset ranged from 5 days to 579 days from initiating selpercatinib. Similarly, no specific patterns in the clinical course of the TEAEs leading to death or in individual patient characteristics were identified. Based on the reported AE terms, the fatal TEAEs are summarized.

Cardiac fatal events

- The 2 patients with TEAEs of myocardial infarction had other risk factors that may have contributed to the events, such as obstruction of main pulmonary artery by metastatic disease or cardiac medical history of hyperlipidemia, hypertension, and stroke.
- In the patient with the TEAE of cardiac arrest, the underlying hypertension and tachycardia at baseline could have contributed towards the fatal event.
- For the TEAE of sudden death, the investigator could not rule out the role of the underlying tumor. In addition, the preceding symptoms of poor appetite, fatigue, and vomiting were potentially suggestive of the patient's worsening general condition.
- All cardiac fatal events except sudden death were deemed as unrelated to selpercatinib by the reporting investigators.

Respiratory fatal events

- Two of the 3 TEAEs of fatal respiratory failure* were associated with potential progressive disease.
- In the remaining TEAE of respiratory failure, an infectious etiology could not be ruled out.

Other fatal event

- In the patient with TEAE of malnutrition, an infectious etiology could not be excluded. The reporting investigator deemed the event of malnutrition as related to selpercatinib even though the causality was stated as inconclusive.

*Includes the patient who died due to the TEAE of Respiratory failure during the crossover period and was considered as related to selpercatinib by the reporting investigator.

The incidence of fatal TEAEs observed in the **selpercatinib arm** for the core study period was similar to that previously observed in the development program. Therefore, although there is an imbalance in fatal TEAEs between the study arms, based on the currently available data, there is insufficient evidence to support a causal association with selpercatinib.

The FDA's Assessment:

FDA agrees with the Applicant's summary of deaths in the Overall Safety Population (n=158).

With the updated descriptive analysis of overall survival (data cut-off date May 1, 2024), FDA requested an updated summary of fatal TEAEs (Table 8.17).

Table 8.17: Updated Summary of Deaths (Data Cut-Off Date 05/01/2024)

	Selpercatinib Arm (N = 158)	Control Arm (N = 98)
Deaths from any cause, N (%)	49 (31)	24 (25)
Fatal TEAEs, N (%)	9 (6)	2 (2)
Suicide, N	1*	0
"Death", N	1*	0
Sudden death, N	1	1*
Cardiac arrest, N	1	1*
Malnutrition, N	1	0
Myocardial infarction, N	2	0
Respiratory failure, N	2	0

*New death reported after 05/01/2023 data cut-off

Source: Applicant's response to FDA Information Request dated June 3, 2024

FDA reviewed the narratives for each fatal treatment-emergent adverse event (TEAE) across the two study arms (Table 8.18). Seven of 9 fatal TEAEs that occurred on the selpercatinib arm appeared unlikely to be related to selpercatinib, but rather to progressive disease, infection, aspiration events, or underlying cardiac risk factors. There was limited available information for the remaining two fatal TEAEs, so it is challenging to rule out the potential contribution of selpercatinib to these events (one sudden death and one suicide).

The two fatal TEAEs that occurred on the control arm occurred after crossover to selpercatinib. Both deaths appeared to be due to underlying cardiac risk factors and probably not related to the study treatment (one sudden death and one cardiac arrest).

Overall, fatal TEAEs were uncommon (6% and 2% in the selpercatinib and control arms, respectively). In addition, patients who received standard of care chemotherapy with or without immunotherapy had a shorter median time on treatment with a fixed number of treatment cycles, whereas patients who received selpercatinib continued on treatment indefinitely until progressive disease or unacceptable toxicity. Thus, the likelihood of having a fatal event while on treatment was more likely for patients receiving selpercatinib. Based on the available data, there is no clear evidence to suggest a detriment to overall survival based on toxicity for patients receiving selpercatinib.

Table 8.18: FDA Analysis of Fatal Treatment-Emergent AEs in LIBRETTO-431

Selpercatinib Arm (N=9), Patient ID	Fatal TEAE	Narrative	FDA Attribution
(b) (6)	Sudden death	73-year-old male who was a former smoker developed Grade 1 vomiting, Grade 2 decreased appetite, and Grade 3 malaise on Study Day 235. On Study Day 238, he developed sudden incontinence and died at home while eating; no investigations or were autopsy performed.	Limited data, unable to rule out relatedness
	Malnutrition	75-year-old male who was a former smoker with history of pneumonia developed sore throat, difficulty breathing and decreased appetite on Study Day 574. It was reported	Probably not related (likely infectious), but challenging to rule out completely

(b) (6)		that family members had similar symptoms (fever, sore throat). He died 5 days later due to malnutrition, which the investigator attributed as related to study drug; no autopsy was performed.	
	Myocardial infarction	79-year-old male with history of HTN, HLD, stroke, and smoking, developed Grade 5 myocardial infarction on Study Day 7 and died at home; no investigations or autopsy were performed. The investigator attributed the death to underlying cardiac risk factors.	Probably not related (likely secondary to multiple cardiac risk factors)
	Acute respiratory failure	74-year-old male with history of HTN and hypothyroidism developed progressive disease on Study Day 50 with suspected carcinomatous lymphangitis and pleural effusions. He subsequently died on Study Day 60 due to acute respiratory failure; no autopsy was performed.	Unlikely related (likely secondary to progressive disease)
	Respiratory failure	59-year-old male with history of HTN and DM developed Grade 3 prolonged QT on Study Day 37 leading to discontinuation of selpercatinib. He was hospitalized on Study Day 42 for dyspnea and Grade 3 pneumonia treated with antibiotics (no steroids administered) and required mechanical ventilation. Of note, he received methadone from Study Day 27-46 for pain management. He died Study Day 46 due to respiratory failure; no autopsy was performed.	Unlikely related (likely secondary to infectious pneumonia and underlying disease)
	Myocardial infarction	54-year-old male developed progressive disease on Study Day 37 but continued on therapy as clinically benefiting per investigator. On Study Day 70, he had a fatal MI; CT was performed and showed a mass causing obstruction in the main pulmonary artery/right upper lobe; ECG showed ST	Unlikely related (likely due to anatomic location of progressive disease)

(b) (6)		depression. The Investigator assessed the death as not related to the study drug.	
	Cardiac arrest	69-year-old female with history of HTN; on Study Day 5 she vomited the study drug after ingestion and had cardiac arrest at home. Upon arrival at the hospital, she had loss of consciousness and no breathing sounds on the right side; her O2 saturation was 70%; despite CPR, she died due to cardiac arrest at the hospital; no autopsy was performed.	Unlikely related (likely secondary to an aspiration event)
	Suicide	62-year-old male with history of atrial fibrillation, HTN, and pericarditis; attempted suicide at home on Study Day 905. He was hospitalized and died the following day; no additional information on the attempted suicide or clinical status was available.	Limited data, unable to rule out relatedness
	Death	66-year-old male with history of brain metastases and ischemic stroke; he had a fall and femur fracture on Study Day 718 after which surgery was advised but declined per patient/family preference. He received his last dose of selpercatinib on Study Day 729, discontinued due to AE (no evidence of progressive disease). He died at home on SD 739; the death certificate stated lung cancer was the cause of death, and no autopsy was performed.	Unlikely related (likely related to fall and underlying disease)
Control Arm (N=2), Patient ID			
(b) (6)	Sudden Death	67-year-old male with history of HTN, T2DM, diabetic neuropathy, hypercholesterolemia, and former smoker developed progressive disease on the control arm and crossed over to selpercatinib arm on Study Day 524. On crossover Study Day	Probably not related (likely secondary to multiple cardiac risk factors)

(b) (6)		1360, he received last dose of selpercatinib (unclear reason). On Study Day 1373, his ECG showed an ST wave abnormality (anterolateral ischemia). On Study Day 1377, he died suddenly at home; no autopsy was performed; the investigator attributed the death as unrelated to study drug.	
	Cardiac arrest	68-year-old male with history of HTN, T2DM, sinus node dysfunction, and smoking history, completed control arm therapy with stable disease on Study Day 514. He had AEs of decreased appetite, weight loss, and anemia. On Study Day 525, he was found dead at home and cause of death was cardiac arrest per paramedics; no autopsy was performed.	Probably not related (likely secondary to multiple cardiac risk factors)

Source: FDA analysis of data submitted in ADAE datasets, narrative summaries, and Applicant's response to FDA Information Request dated June 3, 2024

Serious Adverse Events

Data:

A higher overall frequency of treatment-emergent serious adverse events was reported in patients in the **selpercatinib arm** versus the **control arm** (34.8% versus 23.5%).

The most frequently reported (≥2%) any-Grade SAEs by PT in the **selpercatinib arm** were

- Pleural effusion (4.4%), and
- Hepatic function abnormal (2.5%).

The most frequently reported (≥2%) any-Grade SAEs by PT in the **control arm** were

- Anemia (2.0%)
- Intestinal obstruction (2.0%)
- Neutropenia (2.0%)
- Platelet count decreased (2.0%)
- Pneumonia (2.0%)
- Pyrexia (2.0%), and
- Spinal cord compression (2.0%).

The Applicant's Position:

Based on the SAEs reported in the LIBRETTO-431 **Safety-Overall Population**, a higher frequency was observed in the **selpercatinib arm** compared to the **control arm**.

The FDA's Assessment:

FDA agrees with the Applicant's position. Serious adverse reactions occurred in 35% of patients who received selpercatinib. The most frequent serious adverse reactions (≥2% of patients) were pleural effusion (4.4%, 7 patients) and abnormal hepatic function (2.5%, 4 patients).

The serious adverse reactions in the control arm were predominately related to myelosuppression.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

A higher percentage of patients experienced TEAEs that led to treatment discontinuation in the **selpercatinib arm** compared with the **control arm** (10.1% versus 2.0%).

In the **selpercatinib arm**, except for ALT increased and myocardial infarction that were experienced by 2 patients each, the TEAEs resulting in treatment discontinuation were reported in 1 patient each.

A total of 2% of patients in the **control arm** had TEAEs resulting in treatment discontinuation. The TEAEs resulting in treatment discontinuation were reported in 1 patient each and included intestinal obstruction and neutrophil count decreased.

Discontinuations in the **selpercatinib arm** were observed in patients who developed TEAEs of Myocardial infarction, Cardiac arrest, Sudden death, Acute respiratory failure, and Malnutrition due to fatal outcomes.

The Applicant's Position:

The majority of patients who experienced AEs were able to remain on study treatment due to dose adjustments.

The FDA's Assessment:

FDA agrees with the Applicant's position that discontinuations were more common in the selpercatinib arm. Permanent discontinuation due to an adverse reaction occurred in 10% of patients who received selpercatinib. Adverse reactions resulting in permanent discontinuation in ≥1% of patients included increased ALT (1.3%), and myocardial infarction (1.3%). As stated in the section above, patients who received standard of care chemotherapy with or without

immunotherapy had a shorter median time on treatment with a fixed number of treatment cycles, whereas patients who received selpercatinib continued on treatment indefinitely until progressive disease or unacceptable toxicity. Thus, the likelihood of discontinuing treatment due to an adverse event was more likely for patients receiving selpercatinib.

Dose Interruption/Reduction Due to Adverse Effects

Data:

The study protocol instructed investigators on dose reductions, dose delays, and dose omissions (withheld) for specific AEs and allowed dose modifications at the discretion of the treating physician.

All dose modifications are reported based on PTs and not composite terms.

Table 8.19 summarizes the TEAEs leading to dose adjustments in the **Safety-Overall Population**. Overall, a similar proportion of patients in the **selpercatinib arm** and **control arm** required dose adjustments (77.8% versus 75.5%).

Table 8.19. Summary of Drug Adjustments due to TEAEs
Safety-Overall Population
Core Study Period

Number of Patients	Selpercatinib Arm N=158 n (%)	Control Arm (N=98) n (%)				
		Carboplatin	Cisplatin	Pembrolizumab	Pemetrexed	Any
Patients with at least 1 dose adjustment	123 (77.8)	31 (31.6)	9 (9.2)	50 (51.0)	70 (71.4)	74 (75.5)
Patients with a dose reduction	81 (51.3)	16 (16.3)	2 (2.0)	0[a]	22 (22.4)	28 (28.6)
AEs leading to dose reduction	80 (50.6)	13 (13.3)	2 (2.0)	0	22 (22.4)	25 (25.5)
Patients with a dose delay	NA	17 (17.3)	9 (9.2)	38 (38.8)	45 (45.9)	50 (51.0)
AEs leading to dose delays		12 (12.2)	7 (7.1)	31 (31.6)	34 (34.7)	39 (39.8)
Patients with a dose withheld/omission	120 (75.9)	3 (3.1)	0	22 (22.4)	32 (32.7)	37 (37.8)
AEs leading to dose withheld/omission	113 (71.5)	2 (2.0)	0	7 (7.1)	9 (9.2)	11 (11.2)

Abbreviations: AE = adverse event; N = number of patients; n = number of patients in the specific category; NA = not applicable; TEAE = treatment-emergent adverse event.

[a] No dose reductions were permitted for pembrolizumab.

Dose Reduction

In the **selpercatinib arm**, the most frequent TEAEs leading to dose reductions were

- ALT increased: 15.8%, and
- AST increased and ECG QT prolonged: 6.3%, each.

In the **control arm**,

- dose reductions of pembrolizumab were not permitted, per protocol, and
- no TEAE led to dose reduction of carboplatin, cisplatin, or pemetrexed in 5% or more of patients.

Dose Delay

In the **selpercatinib arm**, dose delay was not applicable, as selpercatinib was administered orally and BID. Therefore, no dose delays were observed in the **selpercatinib arm**.

In the **control arm**, 39.8% of patients required a dose delay. The most frequent TEAEs leading to dose delays of pembrolizumab and pemetrexed in 5% or more of patients were

- anemia (pembrolizumab 7.1%, pemetrexed 9.2%), and
- neutropenia (pembrolizumab 5.1%, pemetrexed 6.1%).

No TEAEs led to dose delays of carboplatin and cisplatin in 5% or more of patients.

Dose Witheld/Omission

In the **selpercatinib arm**, the most frequent TEAEs leading to dose withheld were

- ALT increased: 18.4%
- Hypertension: 8.9%, and
- AST increased and ECG QT prolonged: 7.0%, each.

In the **control arm**,

- no TEAEs led to dose omission of cisplatin, and
- no TEAE led to dose omission of carboplatin, pembrolizumab, or pemetrexed in 5% or more of patients.

The Applicant's Position:

The percentage of patients requiring a dose adjustment was comparable between arms. Dose reductions and/or withholds in the **selpercatinib arm** occurred more often than in the **control arm**. The majority of the dose reductions and/or withholds were related to laboratory abnormalities and ECG QT prolongation, which are recognized ADRs for selpercatinib. Dose delays occurred frequently in the **control arm**.

The FDA's Assessment:

FDA agrees with the Applicant's position that dosage modifications were common on both arms (>75% of patients in both arms).

Dosage interruptions due to an adverse reaction occurred in 72% of patients who received selpercatinib. Adverse reactions requiring dosage interruption in ≥5% of patients included increased ALT (18%), hypertension (9%), increased AST (7%), QT prolongation (7%), diarrhea (5%), and COVID-19 infection (5%).

Dose reductions due to an adverse reaction occurred in 51% of patients who received selpercatinib. Adverse reactions requiring dose reductions in ≥5% of patients included increased ALT (16%), increased AST (6%), and QT prolongation (6%).

Significant Adverse Events

The Applicant's Position:

Significant AEs are reported and described in SAEs preceding this section, and in the following Treatment-Emergent Adverse Events and Adverse Reactions paragraph and in Section 8.2.5 AESIs.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Treatment-Emergent Adverse Events and Adverse Reactions

Treatment-emergent adverse events

Data:

Table 8.20 provides an overview of AEs in the **selpercatinib arm** and **control arm** of the **Safety-Overall Population** during the core study period.

Table 8.20. Overview of Adverse Events
Safety-Overall Population
Core Study Period

Number of Patients[a]	Selpercatinib Arm N=158 n (%)	Control Arm N=98 n (%)
Median time on treatment, months	**16.7**	**9.8**
Any TEAE	**158 (100.0)**	**97 (99.0)**
Related to study treatment[b]	149 (94.3)	92 (93.9)

Number of Patients[a]	Selpercatinib Arm N=158 n (%)	Control Arm N=98 n (%)
Grade ≥3 TEAE	**111 (70.3)**	**56 (57.1)**
Related to study treatment[b]	89 (56.3)	41 (41.8)
Any SAE	**55 (34.8)**	**23 (23.5)**
Related to study treatment[b]	30 (19.0)	14 (14.3)
AE leading to permanent treatment discontinuation	**16 (10.1)**	**2 (2.0)**
Related to study treatment[b]	11 (7.0)	2 (2.0)
SAE leading to permanent treatment discontinuation[c]	**8 (5.1)**	**1 (1.0)**
Related to study treatment[b]	4 (2.5)	1 (1.0)
Fatal AEs[d]	**7 (4.4)**	**0**
Fatal AE on study treatment	6 (3.8)	0
Related to study treatment[e]	2 (1.3)	0
Fatal AE within 30 days of last dose	1 (0.6)	0
Related to study treatment[b]	0	0

Abbreviations: AE = adverse event; N = number of patients in analysis population; n = number of patients in specified category; SAE = serious adverse event.; TEAE = treatment-emergent adverse event.

a Patients may be counted in more than 1 category.

b Include events that were considered related to study treatment as judged by the Investigator.

c Included SAEs without regards to treatment-emergent status.

d Deaths on therapy and within 30 days of last dose date are included. Deaths are also included as SAEs and discontinuations due to adverse events.

e Sudden death and malnutrition.

Safety-Overall

Most frequently occurring any-grade TEAEs in 30% of patients or more in both treatment arms (selpercatinib versus control) were

- *AST increased: 61.4% versus 39.8%*
- *ALT increased: 60.1% versus 39.8%*, and
- *Fatigue: 32.3% versus 50.0%.*

Any-grade TEAEs occurring at higher frequency in selpercatinib arm versus control arm.

The any-grade TEAEs occurring in 15% of patients or more at a 5% or higher point difference in the **selpercatinib arm** compared with the **control arm** were

- *AST increased: 61.4% versus 39.8%*
- *ALT increased: 60.1% versus 39.8%*
- *Hypertension:48.1% versus 7.1%*
- *Diarrhea: 44.3% versus 24.5%*
- *Edema: 41.1% versus 27.6%*
- *Dry mouth: 39.2% versus 6.1%*

- Blood bilirubin increased: 37.3% versus 1.0%
- *Abdominal pain: 25.3% versus 19.4%*
- *Blood creatinine increased: 24.7% versus 17.3%*
- *ECG QT prolonged: 20.3% versus 1.0%*, and
- Hypokalemia: 15.2% versus 8.2%.

All these TEAEs are known ADRs for selpercatinib in the USPI.

Other clinically relevant any-grade TEAEs occurring in less than 15% of patients at a 5% or higher point difference in the **selpercatinib arm** versus **control arm** were

- Hypoalbuminemia: 14.6% versus 6.1%
- Hypocalcemia: 8.2% versus 1.0%
- Pleural effusion: 7.6% versus 1.0%, and
- Ascites: 5.7% versus 0%.

Most of these TEAEs were Grade 1 or 2 in severity.

Any-grade TEAEs occurring at higher frequency in control arm versus selpercatinib arm.

The any-grade TEAEs occurring in 15% of patients or more with at least 5% difference lower in the **selpercatinib arm** compared with the **control arm** were

- *Anemia*: 11.4% *versus* 59.2%
- *Fatigue: 32.3% versus 50.0%*
- *Neutropenia: 22.8% versus 44.9%*
- Nausea: 12.7% versus 43.9%
- *Constipation: 21.5% versus 39.8%*
- *Decreased appetite: 17.1% versus 33.7%*
- *Leukopenia: 25.3% versus 32.7%*
- *Pyrexia: 13.3% versus 23.5%*
- *Vomiting: 12.7% versus 23.5%*, and
- Pruritus: 10.1% versus 22.4%.

Adverse Drug Reactions

Events were classified as ADRs based on predefined core safety information statistical 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.

Based on the safety data from LIBRETTO-431, 2 new ADRs were determined:

- Urinary tract infections, and
- Stomatitis.

Table 8.21 provides detailed information on these new ADRs.

Table 8.21. Summary of Newly Determined ADRs

ADRs	Data Based on Safety-Overall Population (N = 256)
Urinary tract infections	**TEAE Urinary tract infections FMQ narrow terms** The frequency of urinary tract infections in the **Safety-Overall Population** was higher in the **selpercatinib arm (15.2%)** versus the **control arm (7.1%)**. • One Grade 3 SAE of urosepsis was reported (0.6%) and deemed unrelated to selpercatinib. • One patient (0.6%) had a dose omission. • No dose reductions, delays, or permanent discontinuations were reported. Urinary tract infections (based on FMQ Renal and Urinary tract infections – narrow terms) are recommended for inclusion as ADRs due to higher frequencies observed in the **selpercatinib arm**. Although the majority of TEAEs were of low grade in Study JZJC, addition of this event as an ADR may prompt identifying and reporting early signs and symptoms, routine monitoring, and management of low-grade infections, and thus prevent severe or serious outcomes. The frequency of the TEAEs of urinary tract infection observed in LIBRETTO-431 was similar to that observed in the LIBRETTO-001 **NSCLC Population** (23.2%, N = 362) and in the LIBRETTO-001 **Overall Safety Population** (20.2%, N = 837).
Stomatitis	**Stomatitis** (**composite term:** stomatitis, mouth ulceration, mucosal inflammation) The frequency of the composite term *Stomatitis* in the **Safety-Overall Population** was similar in the **selpercatinib arm (17.7%)** versus the **control arm (16.3%).** • No Grade 3 or higher events were reported. • No SAEs were reported. • No dose reductions or dose delays were reported in the **selpercatinib arm**. • Two dose omissions were reported in the **selpercatinib arm** (1.3%). • No permanent discontinuations were reported. Although stomatitis is clinically nonspecific and did not show significant difference in frequencies between the treatment arms, it is a clinically important event, which may have an impact on dose interruptions, especially for an oral agent. Stomatitis can also be considered as a class effect as observed in TKIs with *RET* inhibition and thus is recommended for inclusion as an ADR. The frequency of the TEAEs of *Stomatitis* observed in LIBRETTO-431 was similar to that observed in the LIBRETTO-001 **NSCLC Population** (18.0%, N = 362) and in the LIBRETTO-001 **Overall Safety Population** (17.4%, N = 837).

Abbreviations: ADR = adverse drug reaction; FMQ = FDA Medical Query; JZJC = J2G-MC JZJC; N = number of patients in the analysis population; *RET* = REarranged during Transfection; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TKI = tumor kinase inhibitor.

The Applicant's Position:

No additions to the existing Warnings and Precautions based on these newly determined ADRs are proposed in the USPI. The addition of these 2 ADRs in the USPI did not result in additional pharmacovigilance activities or risk minimization measures. No changes to the risk management plan were warranted due to the labeling updates. No significant impact on the overall benefit-risk profile of selpercatinib is expected due to the newly proposed ADRs.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Overall, the safety profiles of selpercatinib vs. chemo-immunotherapy differed. TEAEs that occurred more commonly in the selpercatinib arm included elevated transaminases (AST, ALT) and bilirubin, hypertension, diarrhea, edema, dry mouth, abdominal pain, increased creatinine, prolonged QT, and hypokalemia. These risks are well-described in the current product labeling for selpercatinib. TEAEs that occurred more commonly in the control arm included myelosuppression (anemia, neutropenia, leukopenia), fatigue, nausea, vomiting, decreased appetite, constipation, pyrexia, and pruritis.

There were more high-grade and serious adverse events on the selpercatinib arm. Notably, patients who receive chemo-immunotherapy have a fixed treatment cycle, whereas patients who receive selpercatinib continue on treatment indefinitely until progressive disease or unacceptable toxicity; this is reflected in a longer median time on treatment (median time on treatment 20.1 months [range 0.2, 44.4] in the selpercatinib arm vs. 10.1 months [range 0.7, 33.7] in the control arm).

In an FDA analysis of patients who received selpercatinib in the crossover phase after progressing on the control arm, there did not appear to be appreciably different toxicity in those patients compared to patients who received selpercatinib alone (Table 8.22).

Table 8.22: Summary of Safety for Patients on Selpercatinib Arm, Control Arm, and those who crossed over to selpercatinib after progressing on the control arm

	Selpercatinib N = 158 n (%)	**Control Arm N = 98 n (%)**	**Crossover to selpercatinib after control arm N=52 n (%)**
Median time on treatment, months (range)	20.1 (0.2, 44.4)	10.1 (0.7, 33.7)	NR
All-cause TEAEs			

Any Grade	158 (100)	98 (100)	51 (98)
Grade ≥ 3	114 (72)	57 (58)	36 (69)
Leading to dose reduction	84 (53)	25 (25)	28 (54)
Leading to permanent discontinuation	16 (10)	3 (3)	6 (12)
SAEs			
Any Grade	58 (37)	24 (25)	19 (37)
Leading to permanent discontinuation	8 (5)	2 (2)	NR

NR=not reported

Source: FDA analysis of ADSL and ADAE datasets

The most common adverse reactions (≥25%) in patients who received selpercatinib were hypertension, diarrhea, edema, dry mouth, rash, fatigue, abdominal pain, and musculoskeletal pain (Table 8.23).

Clinically relevant adverse reactions in <15% of patients who received selpercatinib include headache (14%); hemorrhage (13%); urinary tract infections (12%); hypothyroidism (9%); pneumonia (9%); dizziness (8%); interstitial lung disease/pneumonitis (4.4%); hypersensitivity, chylous ascites, and chylothorax (all < 2%).

Table 8.23: Adverse Reactions (≥15%) in Patients on Either Arm in LIBRETTO-431

Adverse Reaction	**Selpercatinib (n=158)**		**Chemotherapy with or without pembrolizumab (n=98)**	
	Grades 1-4# (%)	**Grades 3-4 (%)**	**Grades 1-4# (%)**	**Grades 3-4 (%)**
Vascular disorders				
Hypertension	48	20*	7	3.1*
Gastrointestinal disorders				
Diarrhea[1]	44	1.3*	24	2.0*
Dry mouth[2]	39	0	6	0
Abdominal pain[3]	25	0.6*	19	2.0*

Constipation	22	0	40	1.0*
Stomatitis[4]	18	0	16	0
Nausea	13	0	44	1.0*
Vomiting[5]	13	0	23	1.0*
General disorders and administration site conditions				
Edema[6]	41	2.5*	28	0
Fatigue[7]	32	3.2*	50	5*
Pyrexia	13	0.6*	23	0
Skin and subcutaneous tissue disorders				
Rash[8]	33	1.9*	30	1.0*
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[9]	25	0	28	0
Investigations				
Electrocardiogram QT prolonged	20	9*	1.0	0
Metabolism and nutrition disorders				
Decreased appetite	17	0	34	2.0*
Infections and infestations				
COVID19 infection	19	0.6*	18	0

[1] Diarrhea includes diarrhea, anal incontinence.

[2] Dry mouth includes dry mouth, mucosal dryness.

[3] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, gastrointestinal pain.

[4] Stomatitis includes stomatitis, mouth ulceration, mucosal inflammation.

[5] Vomiting includes vomiting, retching, regurgitation.

[6] Edema includes edema, edema peripheral, face edema, periorbital edema, swelling face, peripheral swelling, localized edema, eyelid edema, orbital edema, eye edema, scrotal edema, penile edema, orbital swelling, periorbital swelling.

[7] Fatigue includes fatigue, asthenia, malaise.

[8] Rash includes rash, rash maculopapular, skin exfoliation, rash erythematous, rash macular, dermatitis, urticaria, rash papular, dermatitis allergic, rash pustular, rash vesicular, genital rash.

[9] Musculoskeletal pain includes musculoskeletal pain, arthralgia, back pain, bone pain, musculoskeletal chest pain, non-cardiac chest pain, neck pain, pain in extremity.

* No Grade 4 abnormalities were reported.

[#] Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

Laboratory Findings

Data:

Hematology

Most of the hematology abnormalities observed were Grade 1 or 2.

Selpercatinib arm

Any-grade laboratory abnormalities

Any-grade postbaseline hematology abnormalities occurring in 15% or more of patients in either treatment arm that were reported ***more frequently (>5%-point difference)*** in the **selpercatinib arm** compared to the **control arm** were

- platelet count decreased: 52.6% versus 39.2%, and
- hemoglobin increased: 20.1% versus 1.0%.

Grade 3 or 4 laboratory abnormalities

No Grade 3 or 4 laboratory abnormality was reported more frequently in the **selpercatinib arm** compared to the **control arm**. The only Grade 3 or 4 laboratory abnormality occurring in 5% or more of patients was lymphocyte count decreased (8.4%).

Control arm

Any-grade laboratory abnormalities

Any-grade postbaseline hematology abnormalities occurring in 15% or more of patients that were reported ***less frequently (>5%-point difference)*** in the **selpercatinib arm** compared with the **control arm** were

- anemia: 21.4% versus 90.7%
- lymphocyte count decreased: 52.6% versus 62.9%, and
- white blood cell count decreased: 56.5% versus 61.9%.

Grade 3 or 4 laboratory abnormalities

Grade 3 or 4 postbaseline hematology abnormalities occurring in 5% or more of patients that were reported ***less frequently (>5%-point difference)*** in the **selpercatinib arm** compared to the **control arm** were

- lymphocyte count decreased: 8.4% versus 15.5%
- neutrophil count decreased: 2.0% versus 11.3%
- white blood cell count decreased: 1.3% versus 9.3%, and
- anemia: 0% versus 5.2%.

Serum Chemistry

Selpercatinib arm

Any-grade laboratory abnormalities

Most of the serum chemistry abnormalities observed were Grade 1 or 2.

Any-grade postbaseline serum chemistry abnormalities occurring in 15% or more of patients in either treatment arm that were reported ***more frequently (>5%-point difference)*** in the **selpercatinib arm** compared to **control arm** were

- ALT increased: 80.9% versus 62.9%
- AST increased: 76.9% versus 46.4%
- hypocalcemia: 52.6% versus 23.7%
- blood bilirubin increased: 51.6% versus 9.4%
- alkaline phosphatase increased: 35.0% versus 21.7%
- hypermagnesemia: 26.9% versus 15.5%
- hyperkalemia: 25.8% versus 15.5%
- hypernatremia: 21.8% versus 13.4%
- hypoalbuminemia: 24.8% versus 5.2%, and
- hypomagnesemia: 16.0% versus 8.3%.

Grade 3 or 4 laboratory abnormalities

Grade 3 or 4 postbaseline serum chemistry abnormalities occurring in 5% or more of patients in either treatment arm that were reported ***more frequently (>5%-point difference)*** in the **selpercatinib arm** compared to the **control arm** were

- ALT increased: 21.0% versus 4.1%, and
- AST increased: 9.6% versus 0.0%.

Control arm

Any-grade laboratory abnormalities

Any-Grade postbaseline serum chemistry abnormalities occurring in 15% or more of patients in either treatment arm that were reported ***less frequently (>5%-point difference)*** in the **selpercatinib arm** compared to the **control arm** were

- hyponatremia: 30.8% versus 41.2%, and
- hypercalcemia: 18.0% versus 25.8%.

Grade 3 or 4 laboratory abnormalities

In the **control arm**, no Grade 3 or 4 postbaseline serum chemistry abnormalities occurred in 5% or more of patients.

The Applicant's Position:

The percentage of patients with reported treatment-emergent laboratory abnormalities was higher than the percentage of patients with laboratory abnormalities reported as TEAEs. This is a consequence of sites only reporting laboratory abnormalities that were deemed to be clinically significant by the investigator as AEs.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. The most common Grade 3 or 4 laboratory abnormalities (≥5%) in patients who received selpercatinib were increased ALT, increased AST, and decreased lymphocytes.

Table 8.24 summarizes the laboratory abnormalities in LIBRETTO-431.

Table 8.24: Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients on Either Arm in LIBRETTO-431

Laboratory Abnormality[1]	**Selpercatinib**		**Chemotherapy with or without pembrolizumab**	
	Grades 1-4# (%)	**Grades 3-4 (%)**	**Grades 1-4# (%)**	**Grades 3-4 (%)**
Chemistry				
ALT increased	81	21	63	4.1
AST increased	77	10	46	0
Alkaline phosphatase Increased	35	1.3	22	0
Total bilirubin Increased	52	1.3	9	0
Blood creatinine Increased	23	0	21	0
Magnesium decreased	16	0.6	8	0
Albumin decreased	25	0	5	0
Calcium decreased	53	1.9	24	1.0

Laboratory Abnormality[1]	Selpercatinib		Chemotherapy with or without pembrolizumab	
	Grades 1-4# (%)	Grades 3-4 (%)	Grades 1-4# (%)	Grades 3-4 (%)
Sodium decreased	31	3.2	41	2.1
Potassium decreased	17	1.3	15	1.0
Hematology				
Platelets decreased	53	3.2	39	5
Lymphocyte count decreased	53	8	64	15
Hemoglobin decreased	21	0	91	5
Neutrophil count decreased	53	2.0	58	11

[1] Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available: RETEVMO (range: 154 to 157 patients) and chemotherapy with or without pembrolizumab (range: 96 to 97 patients).

Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

Vital Signs

Data:

Vital sign assessments included

- heart rate
- respiration rate
- temperature
- pulse oximetry
- body weight, and
- blood pressure.

The Applicant's Position:

Abnormal findings in blood pressure are considered as AESIs and were observed in higher frequency in the **selpercatinib arm** than in the **control arm**. No other clinically meaningful differences were observed in other vital signs between treatment arms.

The FDA's Assessment:

FDA agrees with the Applicant's position. No new significant findings were identified in FDA's evaluation of the vital signs dataset. In the Overall Safety Population (n=158), the median weight was 65 kilograms (range 42 to 135). The median heart rate was 80 beats per minute (range 46 to 143). The median temperature 36.6 degrees Celsius (range 34.1 to 38.5). The median systolic blood pressure was 127 mmHg (range 85 to 192), and the median diastolic blood pressure was 80 mmHg (range 43 to 140). Hypertension is a known safety risk with selpercatinib and is included in the Warnings and Precautions section of product labeling.

Electrocardiograms (ECGs)

Data:

A total of 28 (17.9%) patients in the **selpercatinib arm** versus 2 patients (2.1%) in the **control arm** experienced QTc interval greater than 500 msec, an increase greater than 60 msec, or both.

QTc interval greater than 500 msec

- 8 (5.1%) patients in the **selpercatinib arm**, and
- 1 (1.0%) patient in the **control arm**.

QTc interval increase greater than 60 msec

- 26 (16.7%) patients in the **selpercatinib arm**, and
- 2 (2.1%) patients in the **control arm**.

The Applicant's Position:

ECG QT prolongation is considered an AESI and was observed at a higher frequency in the **selpercatinib arm** than in **control arm**. No clinically significant arrhythmias were observed.

The FDA's Assessment:

FDA agrees with the Applicant's position. Refer to the original review dated May 8, 2020 for FDA's in-depth analysis regarding QT prolonging potential. The dedicated QT review found that concentration-dependent QTc prolongation was detected in the thorough QT study.

In the overall safety population (n=158), 20% of patients had any grade TEAE of prolonged QTc interval and 9% 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

Data:

QT prolongation and abnormalities associated with the QT interval are reported and described in Electrocardiograms (ECGs) preceding this section.

The Applicant's Position:

QT prolongation associated with the QT interval are reported and described in Electrocardiograms (ECGs), "The Applicant's Position" preceding this section.

The FDA's Assessment:

Refer to ECG section above.

Immunogenicity

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. AESIs

Data:

The following were determined to be AESIs for the selpercatinib program:

- Liver injury
- Hypertension
- Hypersensitivity, and
- Electrocardiogram QT interval prolongation.

AST increased, ALT increased, Hypertension, Hypersensitivity, and ECG QT prolongation are recognized ADRs for selpercatinib.

Based on the assessment of the **Safety-Overall Population**, any-grade TEAEs of liver injury especially AST, ALT, and bilirubin elevations and the corresponding laboratory abnormalities were reported at frequencies higher than previously observed in the clinical program. Although this was not observed for all Grade 3 or higher liver-related TEAEs, ALT increased showed higher frequency TEAEs which were of Grade 3 or higher than previously observed in the clinical program.

Table 8.25 summarizes the frequency of AESIs in the **Safety-Overall Population**.

Table 8.25. Frequency of Adverse Events of Special Interest

	Safety-Overall Population N = 256			
	Any Grade (%)		**Grade ≥3 (%)**	
	Selpercatinib Arm N = 158	**Control Arm N = 98**	**Selpercatinib Arm N = 158**	**Control Arm N = 98**
Liver injury				
AST increased	61.4	39.8	12.7	1.0
ALT increased	60.1	39.8	22.2	3.1
Hypertension	48.1	7.1	20.3	3.1
Hypersensitivity	1.9	0	0.6	0
ECG QT prolongation	20.3	1.0	8.9	0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECG = electrocardiogram; N = number of patients in the analysis population.

The Applicant's Position:

The AESIs observed are identifiable, monitorable, and manageable with successful dose-modification strategies, which allow most patients who experience these events to continue selpercatinib treatment. The majority of liver toxicities observed in the **selpercatinib arm** of the **Safety-Overall Population** were low grade and were managed with dose adjustments. No cases of hepatic failure or liver injury were identified.

No new or clinically significant information was observed for the other AESIs that would alter previously established profile of these events.

8.2.5.2. Other Notable Events

Other notable events include the AEs within the Warnings and Precautions section of the USPI that are not included in the AESI:

- hemorrhagic events

- tumor lysis syndrome
- risk of impaired wound healing
- embryo-fetal toxicity
- interstitial lung disease/pneumonitis, and
- hypothyroidism.

The FDA's Assessment:

FDA agrees with the Applicant's position. The current product labeling for selpercatinib includes the following Warnings and Precautions: hepatotoxicity, interstitial lung disease/pneumonitis, hypertension, QTc prolongation, hemorrhagic events, hypersensitivity, tumor lysis syndrome, risk of impaired wound healing, hypothyroidism, and embryofetal toxicity.

During the review, no additional warnings were added. Table 8.26 provides a summary of the incidence of treatment-emergent adverse events which are listed in the existing warnings and precautions of product labeling, comparing the LIBRETTO-431 safety population (N=158) to the overall safety population in current product labeling (N=796).

Regarding hepatotoxicity, elevations of transaminases were observed in the selpercatinib arm more often than the control arm. There was one patient with a Grade 1 event of drug-induced liver injury (reported as not related to selpercatinib); the event was characterized by Grade 1 elevations of transaminases and did not meet the Hy's law criteria. While there were more patients who experienced lab abnormalities of increased AST/ALT in LIBRETTO-431 compared to the overall safety population in current product labeling for selpercatinib, there did not appear to be long term consequences of these lab value changes there were no Grade 4 or 5 TEAEs of hepatotoxicity, and no events of hepatic failure or other related end-organ damage.

Regarding interstitial lung disease (ILD)/pneumonitis, 4 patients had treatment-emergent adverse events of ILD or pneumonitis; 3 additional patients had adverse events that were included in the broad standardized MedDRA query for ILD, including one event of radiation pneumonitis, one event of lung infiltration, and one event of cystic lung disease. All events were Grade 1 or 2 except one Grade 3 event of ILD in a 63-year-old Asian male who developed the event on Study Day 89 and selpercatinib was discontinued; the investigator attributed the event as related to selpercatinib. There were no Grade 4 or 5 events of ILD/pneumonitis. The slightly higher incidence of ILD in this trial compared to current product labeling is likely due to the fact that the overall safety population includes patients with advanced solid tumors other than lung cancer, whereas LIBRETTO-431 only included patients with NSCLC whose underlying disease puts them at risk for pulmonary dysfunction.

Regarding hemorrhagic events, 13% of patients experienced TEAEs within the grouped term of hemorrhage, including events of conjunctival hemorrhage (n=1), epistaxis (n=5), gingival bleeding (n=1), hematemesis (n=1), hematoma (n=2), hematuria (n=5), hemoptysis (n=2), intracranial hemorrhage (n=1), rectal hemorrhage (n=1), retinal hemorrhage (n=1), and vaginal hemorrhage (n=1). All events were Grade 1 except for one Grade 2 event of intracranial hemorrhage.

There were no adverse events related to the potential risks of tumor lysis syndrome, impaired wound healing, or embryofetal toxicity.

Table 8.26: FDA Summary of TEAEs listed in Warnings and Precautions of product labeling, LIBRETTO-431 safety population (N=158) vs. overall safety population (N=796)

Adverse Event of Interest	**LIBRETTO-431 (N=158)**		**Overall Safety Population in Current Product Label (N=796)**	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Hepatotoxicity				
Increased AST	77	10	59	11
Increased ALT	81	21	56	12
Interstitial lung disease/pneumonitis	4.4	0.6	1.8	0.3
Hypertension	48	20	41	20
QTc prolongation	20	9	21	4.8
Hemorrhagic events	13	0	22	2.6
Hypersensitivity	1.9	0.6	6	1.9
Hypothyroidism	9	0	13	0

Source: FDA analysis of ADSL and ADAE datasets, and US product labeling for selpercatinib (RETEVMO)

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Refer to Section 8.1.2 entitled "Secondary or exploratory COA (PRO) endpoints".

8.2.7. Safety Analyses by Demographic Subgroups

Data:

In LIBRETTO-431, patients were stratified based on geography (East Asian versus non-East Asian). Regional distribution was not equal within the **selpercatinib arm** (91 East Asian patients versus 67 non-East Asian patients). Regional differences in the AE profile were observed. East Asian patients in the **selpercatinib arm** had an increased incidence of TEAEs, including liver events, hematological events, increased creatinine, hypertension, and QT prolongation, compared with non-East Asian patients.

Supportive analyses were performed to assess the safety and tolerability of selpercatinib across selected subgroup populations, namely age, gender, and race.

Overall, no notable differences were observed between genders in LIBRETTO-431 in the **selpercatinib arm** except in the following safety topics:

- **Renal and Urinary tract infections**: Higher frequency was observed in female patients compared with male patients (25.9% versus 4.1%); this is expected as seen in the general population
- **Stomatitis**: Higher frequency was observed in female patients compared with male patients (16.5% versus 6.8%)
- **Weight increased**: Higher frequency was observed in male patients compared with female patients (20.5% versus 9.4%), and
- **Alopecia**: Higher frequency was observed in female patients than in male patients (12.9% versus 0.0%).

The Applicant's Position:

No notable numerical differences by region, race or gender were observed between the patient populations enrolled in the **selpercatinib** and **control arms** of LIBRETTO-431.

Although numerical differences are noted by age (younger than 65 years and 65 years and older), these differences are not considered to be clinically significant.

The FDA's Assessment:

FDA agrees with the Applicant's position. High-grade TEAEs were numerically more common in female patients, patients ≥ 65 years of age, and patients enrolled in an East Asian region (Table 8.27). However, is challenging to draw definitive conclusions regarding differential safety as the study was not statistically powered to detect such differences.

Table 8.27: FDA Analysis of All Grade and High-Grade TEAEs in Patients in Selpercatinib Arm of LIBRETTO-431 by Demographic Subgroup

	All Grade TEAEs, N (%)	Grade ≥ 3 TEAEs,

		N (%)
Sex		
Male	73 (100)	50 (68)
Female	85 (100)	61 (72)
Age Group		
< 65 years	99 (100)	67 (68)
≥ 65 years	59 (100)	44 (75)
Geographic Region		
East Asian	91 (100)	70 (77)
Non-East Asian	67 (100)	41 (61)

Source: FDA analysis based on ADAE and ADSL datasets

8.2.8. Specific Safety Studies/Clinical Trials

Data:

Not applicable.

The Applicant's Position:

No specific studies were conducted to evaluate safety concerns.

The FDA's Assessment:

Not applicable

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable

Human Reproduction and Pregnancy

Data:

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.

The Applicant's Position:

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 are available. 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 assessment. US product labeling for selpercatinib includes a warning for embryo-fetal toxicity.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Not applicable. No new information is provided in the current submission.

The FDA's Assessment:

FDA agrees with the Applicant's position that no new information regarding pediatric data is provided in the current submission. Refer to sNDA 213246 Supplement 12 for the safety and efficacy information which supports the use of selpercatinib in certain pediatric patients.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

Overdose:

The highest planned dose of selpercatinib in LIBRETTO-431 was a total daily dose of 320 mg given as 160 mg BID (100% of the recommended Phase 2 dose).

To the Sponsor's knowledge, no clinically significant adverse effects were reported as a result of overdose in LIBRETTO-431.

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.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

Selpercatinib was first authorized by the FDA on 08 May 2020 and has been granted marketing authorization in 40 countries. Selpercatinib is currently authorized for certain patients with

- *RET* fusion-positive NSCLC
- *RET* fusion-positive TC
- *RET*-mutant MTC, and
- *RET* fusion-positive tissue-agnostic solid tumors.

The most recent periodic safety update report had a data lock of 08 May 2023. Specific patient populations and dosing guidance vary by country. Cumulatively, up to 30 April 2023, more than 3800 patients were exposed to selpercatinib worldwide in the postmarketed setting.

The Applicant's Position:

The data reported from the postmarketing setting are generally consistent with the known safety

profile of selpercatinib. Most events were reported as nonserious, and the most frequently reported events were recognized ADRs for selpercatinib or clinically expected in the target population.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Overall, no new significant safety information has been identified from postmarketing sources. The periodic safety update report or periodic benefit-risk evaluation report confirmed and supported the previously established favorable benefit-risk profile for selpercatinib in the currently approved indications.

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.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

Not applicable.

The FDA's Assessment:

The overall safety population included 158 patients with unresectable locally advanced or metastatic *RET* fusion-positive NSCLC who received selpercatinib as a single agent administered at 160 mg orally twice daily in Study LIBRETTO-431. The evaluation of safety was supported by the safety population characterized in current product labeling, which includes 796 predominantly adult patients with solid tumors from Study LIBRETTO-001. Refer to the original multidisciplinary review of NDA 213246 (May 8, 2020) and the review of supplement 7 (September 22, 2022) for a complete review of the original and updated safety populations for LIBRETTO-001.

In the randomized trial LIBRETTO-431, the adverse events observed in the selpercatinib arm were generally consistent with the current product labeling. In the overall safety population (n=158), the most common adverse reactions (≥25%) in patients who received selpercatinib were hypertension, diarrhea, edema, dry mouth, rash, fatigue, abdominal pain, and musculoskeletal pain. The most common Grade 3 or 4 laboratory abnormalities (≥5%) were increased ALT, increased AST, and decreased lymphocytes. Serious adverse reactions occurred in 35% of patients who received selpercatinib. The most frequent serious adverse reactions (≥2% of patients) were pleural effusion, and abnormal hepatic function. Fatal adverse reactions occurred in 4.4% of patients who received selpercatinib; fatal adverse reactions included myocardial infarction (n = 2), respiratory failure (n = 2), cardiac arrest, malnutrition, and sudden death (n = 1, each). Dosage modifications were common, with dosage interruptions in 72%, dose reductions in 51%, and permanent discontinuation due to an adverse reaction in 10% of patients who received selpercatinib.

The control arm safety population comprised 98 patients who received chemotherapy with or without immunotherapy in LIBRETTO-431. The most common adverse reactions (≥25%) for patients on the control arm included fatigue, nausea, constipation, decreased appetite, rash, and edema. The most common Grade 3 or 4 laboratory abnormalities (≥5%) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, and decreased platelets.

While there were more there were numerically more high-grade adverse events and dosage modifications on the selpercatinib arm compared to the control arm, the median time on treatment was double that of the control arm, and there did not appear to be a clear safety signal that would result in worse overall survival for patients receiving selpercatinib.

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).

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

The statistical assessment of efficacy was based on the submitted data and results of the primary endpoint of BICR-assessed PFS per RECIST 1.1 from a pre-specified interim analysis of PFS comparing treatments with selpercatinib vs. investigator's choice of treatments with pembrolizumab and cisplatin or pembrolizumab and carboplatin (ITT-Pembro population). Since BICR-assessed PFS was statistically significant in the ITT-Pembro population, BICR-assessed PFS was then hierarchically tested when comparing treatments with selpercatinib vs. investigator's choice of treatments with or without pembrolizumab and cisplatin or carboplatin (ITT population). A statistically significant PFS benefit was also observed in the ITT population. FDA's sensitivity analyses of BICR-assessed PFS using different censoring rules and subgroup analyses in selected patient or disease characteristics, as presented under "Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)" in the review above, appeared to be consistent and supportive of the results observed in the primary analysis of the primary endpoint.

There were no major statistical issues with the assessment of the primary endpoint, however there were limitations in the assessment of some of the secondary endpoints of LIBRETTO-431.

1. OS in the ITT population was a secondary endpoint that was hierarchically tested at the time of the BICR-assessed PFS interim analysis. OS was immature in the ITT population with 29% observed IF (50 deaths out of 175 deaths for the final analysis). Additionally, 41% of the control arm patients (42 out of 102) crossed over to the selpercatinib arm. The point estimate of the OS HR exceeded 1.0 (OS HR in ITT [95%CI, p-value]) = 1.04 [(0.58, 1.88), 0.89]. Given the immature OS data, the OS results is likely to be confounded by the relatively high crossover rate of control arm patients. An updated descriptive analysis of OS based on one additional year of follow-up data (DCO: May 01, 2024) resulted in an OS HR of 1.26 (95% CI: 0.78, 2.04) in the ITT population. The observed OS IF at the time of this analysis was 43% and 54% (55 out of 102) of the control arm patients crossed over to the selpercatinib arm. Additionally, of the 159 patients randomized to selpercatinib arm, 41% (65/159) received any post-progression therapy: 23% (36/159) received chemotherapy, immunotherapy, or chemo-immunotherapy treatment and 31% (50/159) received a selective RET inhibitor (selpercatinib or pralsetinib) as any post-progression therapy. Whereas, of the 102 patients randomized to the control arm, 64% (65/102) received any post-progression therapy: 23% (23/102) received chemotherapy, immunotherapy, or chemo-immunotherapy treatment and 64% (64/102) received a selective RET inhibitor (selpercatinib or pralsetinib) as any post-progression therapy. The relatively high cross-over rate along with imbalances in the rates and types of post-progression therapy reduces the interpretability of the OS results. The descriptive analysis of OS in the ITT-

Pembro population at the time of this updated analysis resulted in an OS HR of 1.16 (95% CI: 0.68, 1.98) and should be interpreted with caution.

2. The interpretation of the results of the secondary/exploratory endpoints duration of CNS response or time to CNS progression can be difficult to interpret, as systemic progression does not serve as an event or censoring mechanism for the time-to-event measurement.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The Applicant previously provided substantial evidence of effectiveness of selpercatinib 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, as described in the multidisciplinary review dated September 21, 2022 (sNDA 213246 Supplement 7). The traditional approval was based on objective response rate (ORR) and duration of response (DOR) data, with substantial durability of responses in additional patients supported by consistent ORR results, in both treatment-naïve and previously treated patients with *RET* fusion-positive NSCLC enrolled in Study LOXO-RET-17001 (LIBRETTO-001), an international, single-arm, dose-escalation and multi-cohort expansion study that supported the accelerated approval of selpercatinib. FDA did not require a randomized controlled trial to verify the benefit of selpercatinib for this indication due to the perceived lack of equipoise with high overall response rates with prolonged durations of response in a rare biomarker driven population. However, a randomized trial was conducted by the Applicant and submitted to FDA in this supplemental application with a request to update product labeling with new efficacy results for the same existing indication.

This supplement (sNDA 213246 Supplement 11) provides important information about the effectiveness of selpercatinib not furnished by the studies that provided primary support for effectiveness. Specifically, the results of Study LIBRETTO-431, a multi-regional, open-label, randomized, active-controlled trial of selpercatinib versus platinum-based and pemetrexed chemotherapy with or without pembrolizumab in patients with treatment-naïve *RET* fusion-positive, unresectable locally advanced or metastatic NSCLC, provide information about the nature and size of the treatment effect of selpercatinib in patients with *RET* fusion-positive NSCLC, as well as randomized safety data which complement the existing safety database from single arm trials.

The primary efficacy population included 212 patients enrolled in LIBRETTO-431 with an intent to treat with pembrolizumab if randomized to the control arm (129 into selpercatinib arm and 83 into chemotherapy with pembrolizumab arm). A 13.6-month improvement in progression-free survival (PFS) as determined by a blinded independent review committee (BIRC) according to RECIST v1.1, the major efficacy outcome measure, was observed at the first planned interim

analysis (median PFS: 24.8 months in selpercatinib arm vs. 11.2 months in control arm), with a hazard ratio (HR) of 0.47 (95% Confidence Interval [CI] 0.31, 0.70).

Overall survival (OS) was immature at the time of the PFS interim analysis. At the time of an updated descriptive analysis of OS (43% of prespecified OS events for the final analysis), a total of 49 (31%) and 26 (25%) patients died in the selpercatinib and the control arm, respectively. The OS HR was 1.26 (95% CI: 0.78, 2.04). Overall survival may be affected by the imbalance in post-progression therapies. Of 68 patients on the control arm who had disease progression, 50 patients (74%) received selpercatinib at progression. Of 71 patients on the selpercatinib arm who had disease progression, 16 (23%) received chemotherapy and/or immune checkpoint inhibitor therapy, and 44 (62%) continued receiving selpercatinib.

The review team considered that the benefits of selpercatinib outweighed the risks in the intended population even though the point estimate of the OS HR was greater than 1.0. These considerations included the prior determination of substantial evidence of effectiveness based on a high ORR (>80% in two adequate and well-controlled trials) with substantial durability (>20 months in two adequate and well-controlled trials), a >1 year improvement in PFS compared to chemo-immunotherapy in LIBRETTO-431, with a HR of 0.47 (95% CI: 0.31, 0.70), reduced burden to patients for an oral therapy option compared to combination IV therapies, and supportive safety and efficacy data from another randomized study of selpercatinib in patients with *RET* mutation positive MTC (LIBRETTO-531). Furthermore, the study design of LIBRETTO-431 impacted the interpretability of the overall survival results, primarily in that crossover was permitted and the majority of patients on the control arm went on to receive selpercatinib in the crossover phase of the study or alternatively, a commercially available RET inhibitor off study. In addition, most patients in the selpercatinib arm did not receive standard of care chemo-immunotherapy at any point during their treatment course. Therefore, it is possible that treatment with only one effective therapy (i.e., selpercatinib) as opposed to two effective therapies (i.e., selpercatinib plus chemo-immunotherapy) may impact overall survival. However, the study was not designed to evaluate this question and the data remain immature; therefore, it is challenging to draw definitive conclusions regarding this issue based on the available data. While the safety profiles of selpercatinib vs. chemo-immunotherapy differed, there was no clear evidence that worse toxicity would result in differential overall survival for patients receiving selpercatinib and fatal adverse events on the selpercatinib arm were not clearly attributable to selpercatinib. A post-marketing commitment will be included in the approval letter to obtain final OS results from LIBRETTO-431.

Therefore, the review team recommends inclusion of the results of Study LIBRETTO-431 in the product labeling for selpercatinib as this study provides important information about the effectiveness of selpercatinib not furnished by the studies that provided primary support for effectiveness.

X	X
Primary Statistical Reviewer Arup Sinha, PhD	Statistical Team Leader Xiaoxue Li, 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.

10 Pediatrics

The Applicant's Position:

Selpercatinib was granted orphan drug designations for all approved indications and is exempt from Pediatric Research Equity Act 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**
Section 5.6 Warnings and Precautions, Hypersensitivity	(b) (4)	FDA rejected the new text because the proposed (b) (4) (b) (4)
Section 6.1 Adverse Reactions, Clinical Trials Experience	Add a new subsection and provide interim safety data from LIBRETTO-431 based on the data cutoff date of 01 May 2023 for selpercatinib against a combination of platinum-based pemetrexed chemotherapy with or without pembrolizumab (that is, for the **Safety-Overall Population**).	FDA agrees with the Applicant's proposed text and provided minor revisions for clarity. FDA included additional demographic details of the safety population. FDA adjudicated all numbers in this section.
Section 14.1 Clinical Studies, *RET* Fusion-Positive Non-Small Cell Lung Cancer	Add a new subsection and provide interim efficacy data from LIBRETTO-431 based on the data cutoff date of 01 May 2023 for selpercatinib against a combination of platinum-based pemetrexed chemotherapy with pembrolizumab (**ITT-Pembrolizumab Population**). (b) (4)	FDA provided minor editorial revisions to the Applicant's proposed text. FDA revised the presentation of the (b) (4) FDA declined to (b) (4) (b) (4)

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.

	(b) (4)	FDA recommended inclusion of additional details regarding overall survival results.

Abbreviations: **ITT-Pembrolizumab Population** = patients included in the **ITT Population** who were stratified with the intent to receive pembrolizumab in the event of the **control arm** assignment; NDA = new drug application; NSCLC = non-small cell lung cancer; PD-1 = programmed death-1; PD-L1 = programmed death ligand-1; *RET* = REarranged during Transfection.

The Applicant's Position:

Add new subsections to the labeling for the data from LIBRETTO-431 as described above.

The FDA's Assessment:

The Applicant's proposed text was reviewed and revised by FDA for consistency with 21 Code of Federal Regulations (CFR), labeling guidances and current labeling practices of the Office of Oncologic Diseases.

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 PMC was issued for this application:

Complete survival follow-up of patients in the LIBRETTO-431 trial at 175 deaths to further characterize the efficacy and clinical benefit of selpercatinib in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a *RET* gene fusion.

Refer to the approval letter for milestone dates.

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
□	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	__ Yes _X_ No
□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	__ Yes _X_ No
□	Other considerations (e.g.: PK/PD), if applicable:	__ Yes _X_ No

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

Stacy Shord

16 Division Director (OB)

X

Pallavi Mishra-Kalyani

17 Division Director (Clinical)

X

Nicole Drezner

18 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

19 Appendices

19.1. References

The Applicant's References:

Drilon A, Lin JJ, Fillerion T, et al. Frequency of brain metastases and multikinase inhibitor outcomes in patients with RET-rearranged lung cancers. *J Thorac Oncol*. 2018;13(10):1595-1601. https://doi.org/10.1016/j.jtho.2018.07.004

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19.2. 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 NSCLC in the single study, LIBRETTO-431, included in the sNDA submission.

Covered Clinical Study (Name and/or Number):* LIBRETTO-431 (NCT04194944)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: See Form 3454		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: 0 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)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

The FDA's Assessment:

Financial disclosure information was collected for the investigators and sub-investigators participating in LIBRETTO-431.

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Population PK Analysis

19.4.1.1. Executive Summary

The FDA's Assessment:

An updated PPK model was developed, and the visual predictive check (pcVPC) shows a good agreement between the observed and predicted concentrations, indicating that the model adequately describes selpercatinib exposure in all included participants. The updated model included tumor type as a covariate on CL/F. However, there is a significant overlap in exposure metrics across all 3 tumor types suggesting the impact of tumor type on CL/F is not clinically significant.

19.4.1.2. PPK Assessment Summary

The Applicant's Position:

A population PK and exposure-response analyses for efficacy and safety based on LIBRETTO-431 data will be conducted and provided as supportive information within 3 months of the sNDA submission date as agreed with FDA.

The FDA's Assessment:
See section 19.4.1.4 for reviewer's analysis.

19.4.1.3. PPK Review Issues

Not applicable.

19.4.1.4. Reviewer's Independent Analysis

Population PK (PPK) analysis

Review Summary

The applicant's PPK analysis for selpercatinib[1] was reviwed by FDA[2]. An updated PPK model with study LOXO-RET-17001 (LIBRETTO-001), J2G-MC-JZJC (LIBRETTO-431) and J2G-GH-JZJK, in which parameter estimates are within range of those in the FDA reviewed previous PPK model[3], is acceptable support the current submission as outlined in **Table 1**. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

Table 19.1: Specific Comments on Applicant's Final Population PK model

Utility of the final model			**Reviewer's Comments**
Support applicant's proposed labeling statements about intrinsic a d extrinsic factors	**Intrinsic factor**	Body weight, race, dose, tumor type	The applicant's final model was acceptable.
	Extrinsic factor	NA	NA

[1] loxo-292-dmpk-050 page 62 (link)

[2] REV-SUMMARY-11 (Office Director Review) DARRTS: 05/08/2020 page 358 (link)

[3] REV-SUMMARY-10 (Division Director Review); REV-SUMMARY-13 (Unireview) page 138; DARRTS: 09/21/2022 (link)

Derive exposure metrics for Exposure-response analyses	AUC0-24h, AUC0-24h_10, Cmax, Cmax_10, Cmin, Cmin_10[4]	

Introduction

The primary objectives of applicant's analysis were:

- To assess adequacy of the previous PPK model ((b) (4) ID: ELIL-PMX-SELPERCATINIB-4567) to describe the new PK data from the Study J2G-MC-JZJC (data cutoff date: 1 May 2023) and refine the previous PPK model if necessary.

- Conduct an efficacy E-R analysis with ORR and PFS that include subjects with RET fusion NSCLC from Studies LOXO-RET-17001 (data cutoff date: 13 January 2023) and J2G-MC-JZJC (data cutoff date: 1 May 2023, selpercatinib arm only).

- To conduct a safety E-R analysis of AEs of interest with available AE data from all participants in Studies LOXO-RET-17001 (data cutoff date: 13 January 2023) and J2G-MC-JZJC (data cutoff date: 1 May 2023, selpercatinib arm only). The same analysis was repeated for subjects with RET fusion NSCLC only.

PPK model development

Data

Pharmacokinetic (PK) data from the Study LOXO-RET-17001 (803 subjects),Study J2G-GH-JZJK (77 subjects), and Study J2G-MC-JZJC (190 subjects) were utilized in the updated PPK model shown in **Table 2**. Overall, a total of 9236 concentration observation records from 1070 participants were considered for the analysis. BQL data (482 PK observation) were excluded from

[4] AUC0-24h: area under the plasma concentration-time curve over 24 hours at steady state
AUC0-24h_10: area under the plasma concentration-time curve over 24 hours at steady state averaged over the last 10 doses prior to an efficacy or safety event or the last 10 doses during study 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 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 for subjects who did not have an event

analysis and no outliers that warranted exclusion were detected. Demographic covariate data are summarized in **Table 3** (continuous data) and **Table 4** (categorical data).

Table 19.2: Overview of Studies Included in Analysis

Model	Study	Subjects N (% of Total)	Observations N (% of Total)
PPK analysis	LOXO-RET-17001 J2G-GH-JZJK J2G-MC-JZJC (selpercatinib arm and control arm crossed over to selpercatinib arm)	1070 (100%)	9236 (94.9%)
Efficacy E-R for NSCLC (ORR)	LOXO-RET-17001 J2G-MC-JZJC (selpercatinib arm only) NSCLC only	502 (100%)	NA
Efficacy E-R for NSCLC (PFS)	LOXO-RET-17001 J2G-MC-JZJC (selpercatinib arm only) NSCLC only	504 (100%)	NA
Safety E-R overall	LOXO-RET-17001 J2G-MC-JZJC (selpercatinib arm only) Overall	953 (100%)	NA
Safety E-R for NSCLC	LOXO-RET-17001 J2G-MC-JZJC (selpercatinib arm only) NSCLC only	504 (100%)	NA

Note: The calculation of % of total only applies to the PPK analyses. The efficacy and safety E-R analyses included a single subject response; therefore, the number of observations is the same as the number of subjects. The PPK analysis included data from Studies LOXO-RET-17001 and J2G-GH-JZJK. The efficacy and safety E-R analyses included data from the LOXO-RET-17001 study.

Abbreviations: E-R=exposure-response; N=number; NA=not applicable; NSCLC= non-small lung cancer; ORR=overall response rate; PFS=progression-free survival; PPK=population pharmacokinetic

Source: poppk-02-er-report-for-selpercatinib-in-nsclc-patients, Page 24.

Table 19.3 Summary of Baseline Demographic Data in the PPK Analysis: Continuous Variables

Covariate (Unit)	LOXO-RET-17001 (N=803)	J2G-GH-JZJK (N=77)	J2G-MC-JZJC (N=190)[a]	Overall (N=1070)
Age (years)				
Mean	57.4	50.6	59.7	57.3
SD	14.1	12.9	11.3	13.7
Median	59.0	54.0	61.0	58.0
Range	15-92	19-72	31-87	15-92
N	803	77	190	1070
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Body weight (kg)				
Mean	71.0	64.1	66.1	69.7
SD	19.6	13.6	14.6	18.6
Median	67.3	61.5	63.9	65.9
Range	26.8-179	42-108	42-136	26.8-179
N	803	77	190	1070
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Body mass index (kg/m^2)				
Mean	24.9	23.1	24.4	24.7
SD	5.8	3.7	4.48	5.47
Median	23.9	22.7	23.6	23.6
Range	11.6-59.1	16.1-36.3	16.4-43.7	11.6-59.1
N	781	77	188	1046
Missing	22 (2.7%)	0 (0.0%)	2 (1.1%)	24 (2.2%)
Body surface area (m^2)				
Mean	1.8	1.7	1.72	1.77
SD	0.26	0.2	0.21	0.25

Covariate (Unit)	LOXO-RET-17001 (N=803)	J2G-GH-JZJK (N=77)	J2G-MC-JZJC (N=190)*	Overall (N=1070)
Median	1.77	1.7	1.7	1.74
Range	1.1-2.8	1.4-2.3	1.35-2.46	1.11-2.79
N	781	77	188	1046
Missing	22 (2.7%)	0 (0.0%)	2 (1.1%)	24 (2.2%)
Creatinine clearance (mL/min)				
Mean	97.5	104.6	92.7	97.1
SD	45.3	36.0	31.5	42.6
Median	91.0	101.0	87.0	91.0
Range	20.7-762	31.2-281.1	37.9-247	20.7-762
N	803	77	190	1070
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ALT (U/L)				
Mean	25.3	22.0	20.0	24.1
SD	18.5	14.8	11.5	17.3
Median	20	16.2	16.0	19.0
Range	4-158	4-80	6-78	4-158
N	803	77	190	1070
Missing	0 (0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AST (U/L)				
Mean	28.0	25.2	21.5	26.6
SD	19.5	13.9	9.22	17.9
Median	23.0	21.0	20.0	22.0
Range	6-233	9.5-78	10-83.3	6-233
N	803	77	189	1069
Missing	0 (0%)	0 (0.0%)	1 (0.5%)	1 (0.1%)

Covariate (Unit)	LOXO-RET-17001 (N=803)	J2G-GH-JZJK (N=77)	J2G-MC-JZJC (N=190)*	Overall (N=1070)
Bilirubin (mg/dL)				
Mean	9.86	4.0	9.44	9.36
SD	5.71	2.2	5.04	5.62
Median	8.55	3.5	8.75	8.55
Range	2.5-56.4	1.12-12.6	3-28.3	1.12-56.4
N	803	77	190	1070
Missing	0 (0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: ELIL-PMX-SELPERCATINIB-5424_EDA.Rmd

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; N=number of subjects; PPK=population pharmacokinetic(s); SD=standard deviation

* including N= 150 subjects from the selpercatinib arm and N=40 subjects from the control arm crossed over to the selpercatinib arm.

Source: poppk-02-er-report-for-selpercatinib-in-nsclc-patients, Page 26-28.

Table 19.4. Summary of Baseline Demographic Data in the PPK Analysis: Categorical Variables

Covariate	Category	LOXO-RET-17001 (N=803)	J2G-GH-JZJK (N=77)	J2G-MC-JZJC (N=190)*	Overall (N=1070)
Subject-specific categorical covariates					
Sex, N (%)	Male	411 (51.2)	44 (57.1)	84 (44.2)	539 (50.4)
	Female	392 (48.8)	33 (42.9)	106 (55.8)	531 (49.6)
Race, N (%)	Caucasian	543 (67.6)	0 (0)	63 (33.2)	606 (56.6)
	Black or African American	26 (3.2)	0 (0)	2 (1.1)	28 (2.6)
	Asian	193 (24.0)	77 (100)	114 (60)	384 (35.9)
	American Indian/Alaskan Native	2 (0.3)	0 (0)	3 (1.6)	5 (0.5)
	Native Hawaiian or Other Pacific Islander	1 (0.1)	0 (0)	0 (0)	1 (0.1)
	Other	32 (4.0)	0 (0)	0 (0)	32 (3.0)
	Missing	6 (0.7)	0 (0)	7 (3.7)	13 (1.2)
Japanese ethnicity, N (%)	No	718 (89.4)	77 (100)	172 (90.5)	967 (90.4)
	Yes	85 (10.6)	0 (0)	18 (9.5)	103 (9.6)
Chinese ethnicity, N (%)	No	803 (100)	0 (0)	117 (61.6)	920 (86.0)
	Yes	0 (0)	77 (100)	73 (38.4)	150 (14.0)
Asian ethnicity, N (%)	No	604 (75.2)	0 (0)	69 (36.3)	673 (62.9)
	Yes	193 (24.0)	77 (100)	114 (60)	384 (35.9)
	Missing	6 (0.7)	0 (0)	7 (3.7)	13 (1.2)
H2 receptor blocker, N (%)	No	504 (62.8)	76 (98.7)	165 (86.8)	745 (69.6)
	Yes	299 (34.1)	1 (1.3)	25 (13.2)	325 (30.4)
Proton pump inhibitor, N (%)	No	653 (81.3)	73 (94.8)	131 (68.9)	857 (80.1)
	Yes	150 (18.7)	4 (5.2)	59 (31.1)	213 (19.9)
H2 receptor blocker or proton pump inhibitor, N (%)	No	437 (54.4)	72 (93.5)	119 (62.6)	628 (58.7)
	Yes	366 (45.6)	5 (6.5)	71 (37.4)	442 (41.3)

Covariate	Category	LOXO-RET-17001 (N=803)	J2G-GH-JZJK (N=77)	J2G-MC-JZJC (N=190)*	Overall (N=1070)
Weak CYP3A4 inhibitor, N (%)	No	645 (80.3)	77 (100)	189 (99.5)	912 (85.2)
	Yes	158 (19.7)	0 (0)	1 (0.5)	158 (14.8)
Moderate CYP3A4 inhibitor, N (%)	No	656 (81.7)	75 (97.4)	174 (91.6)	905 (84.6)
	Yes	147 (18.3)	2 (2.6)	16 (8.4)	165 (15.4)
Strong CYP3A4 inhibitor, N (%)	No	744 (96.4)	77 (100)	188 (98.9)	1039 (97.1)
	Yes	29 (3.6)	0 (0)	2 (1.1)	31 (2.9)
Any CYP3A4 inhibitor, N (%)	No	529 (65.9)	75 (97.4)	171 (90)	775 (72.4)
	Yes	274 (34.1)	2 (2.6)	19 (10)	295 (27.6)
Weak CYP3A4 inducer, N (%)	No	803 (100)	77 (100)	190 (100)	1070 (100)
	Yes	0 (0)	0 (0)	0 (0)	0 (0)
Moderate CYP3A4 inducer, N (%)	No	800 (99.6)	77 (100)	190 (100)	1067 (99.7)
	Yes	3 (0.4)	0 (0)	0 (0)	3 (0.3)
Strong CYP3A4 inducer, N (%)	No	800 (99.6)	77 (100)	189 (99.5)	1066 (99.6)
	Yes	3 (0.4)	0 (0)	1 (0.5)	4 (0.4)
Any CYP3A4 inducer, N (%)	No	797 (99.3)	77 (100)	189 (99.5)	1063 (99.3)
	Yes	6 (0.7)	0 (0)	1 (0.5)	7 (0.7)
Tumor type, N (%)	RET-mutant MTC	312 (38.9)	26 (33.8)	0 (0)	338 (31.6)
	RET-fusion NSCLC	354 (44.1)	26 (33.8)	190 (100)	570 (53.3)
	RET fusion TC	62 (7.7)	0	0 (0)	62 (5.8)
	Other	75 (9.3)	25 (32.5)	0 (0)	100 (9.3)
First dose (mg), N (%)	20	16 (2.0)	0 (0)	0 (0)	16 (1.5)
	40	16 (2.0)	0 (0)	0 (0)	16 (1.5)
	60	12 (1.5)	0 (0)	0 (0)	12 (1.1)
	80	20 (2.5)	0 (0)	3 (1.6)	23 (2.1)
	120	18 (2.2)	0 (0)	0 (0)	18 (1.7)

Covariate	Category	LOXO-RET-17001 (N=803)	J2G-GH-JZJK (N=77)	J2G-MC-JZJC (N=190)*	Overall (N=1070)
	160	712 (88.7)	77 (100)	187 (98.4)	976 (91.2)
	200	3 (0.4)	0 (0)	0 (0)	3 (0.3)
	240	6 (0.7)	0 (0)	0 (0)	6 (0.6)
Subject nonspecific categorical covariates					
Dose[a] (mg), N (%)	20	19 (2.0)	0 (0)	0 (0)	19 (1.3)
	40	33 (3.4)	12 (9.4)	27 (8.4)	72 (5.1)
	60	36 (3.7)	0 (0)	0 (0)	36 (2.5)
	80	71 (7.3)	18 (14.1)	57 (17.8)	146 (10.3)
	120	41 (4.2)	21 (16.4)	46 (14.4)	108 (7.6)
	160	760 (78.4)	77 (60.2)	189 (59.1)	1026 (72.4)
	200	3 (0.3)	0 (0)	0 (0)	3 (0.2)
	240	6 (0.6)	0 (0)	0 (0)	6 (0.4)
	360	0 (0)	0 (0)	1 (0.3)	1 (0.1)

Source: ELIL-PMX-SELPERCATINIB-5424_EDA.Rmd

[a] The percentage of subjects does not add up 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; MTC=medullary thyroid cancer; N=number of subjects; NSCLC=non-small cell lung cancer; PPK=population pharmacokinetic; RET=rearranged during transfection; TC=thyroid cancer

* including N= 150 subjects from the selpercatinib arm and N=40 subjects from the control arm crossed over to the selpercatinib arm.

Source: poppk-02-er-report-for-selpercatinib-in-nsclc-patients, Page 29-31.

Software and estimation methods

Data manipulation, visualization, and simulations were conducted using R version 4.2.3. PPK analyses were conducted using NONMEM® version 7.5.1.

Final Model

A PPK model including two-compartment disposition, sequential zero- and first-order absorption, and first-order elimination adequately described the plasma concentration-time profile. Parameter estimates for the final PPK model was listed in **Table 19.5**. The goodness of fit plots was shown in **Figure 1**. The prediction corrected pcVPC plot for the final covariate model with all data is shown in **Figure 2**.

Table 19.5. Table 11 NONMEM parameter estimates for the Final Model

	Estimate		Interindividual Variability		
Parameter (Unit)	**Typical Value**	**%RSE**	**Typical Value**	**%RSE**	**Shrinkage[a]**
CL/F (L/h)	5.4	2.4	45%	30	4%
Effect of dose on CL/F (%/mg)	-0.25	184	–	–	–
Effect of MTC tumor type on CL/F (%)[b]	18	23	–	–	–
Effect of other tumor types on CL/F (%)[b]	11	49	–	–	–
Effect of Asian race on F_{rel} (%)	16	20	–	–	–
Q/F (L/h)	31	7.5	–	–	–
Vc/F (L)	104	5.7	69%	7.6	38%
Vp/F (L)	93	4.4	–	–	–
ka (1/h)	1.4	8.4	73%	12	60%
Dur (h)	1.1	4.4	57%	5.8	57%
Residual variability					
Proportional residual error	26%	16	–	–	8.7%
Additive residual error SD (ng/mL)	55	33	–	–	8.7%

Source: run32.lst

[a] Shrinkage (%) was calculated as 100×(1−SD of post hoc/estimated variance).

[b] The reference tumor type is NSCLC+TC.

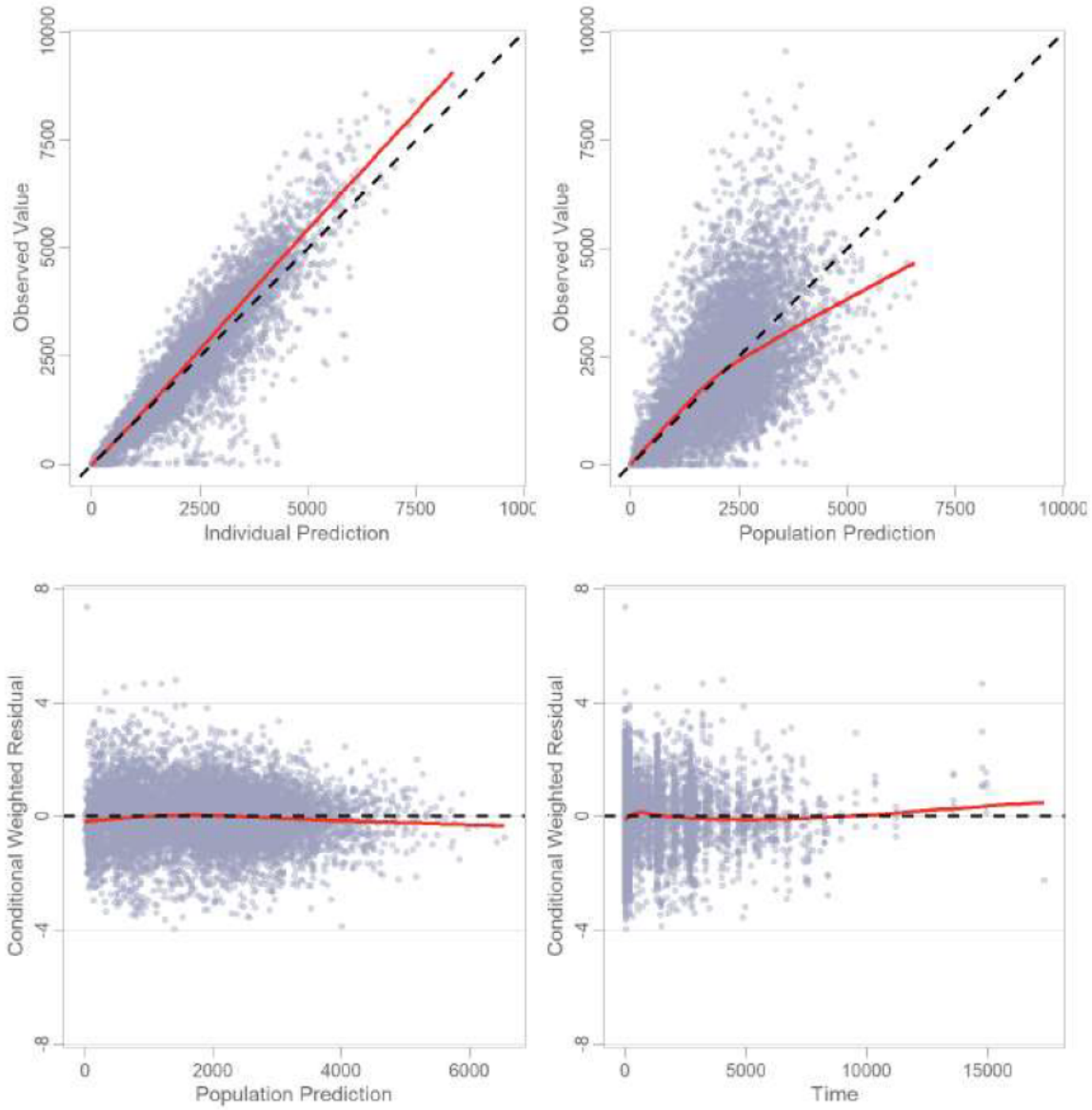
Population estimate of CL = population estimate of CL x effect of tumor type Effect of tumor type = 1 (reference)

Effect of MTC tumor type = 1 (reference) + effect estimate (MTC) Effect of other tumor type = 1 (reference) + effect estimate (other)

Abbreviations: CL/F=apparent clearance; Dur=duration of zero-order absorption; F_{rel}=relative bioavailability; IIV=interindividual variability; ka=absorption rate constant; MTC= medullary thyroid cancer; PK=pharmacokinetic; Q/F=apparent distributional clearance; RSE=relative standard error; SD=standard deviation; Vc/F=apparent central volume of distribution; Vp/F=apparent peripheral volume of distribution

Source: poppk-02-er-report-for-selpercatinib-in-nsclc-patients, Page 45

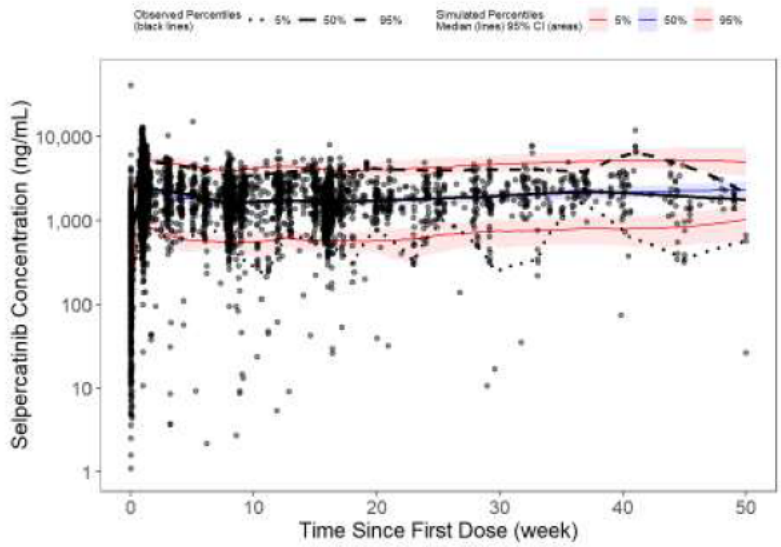
Figure 19.1. Goodness-of-Fit Plots for the Selpercatinib Final PPK Model



Source: ELIL-PMX-SELPERCATINIB-5424_GOF_run32.Rmd
Note: Black line is the identity line. Red line is the LOESS.
Abbreviations: LOESS=locally estimated scatterplot smoothing; PPK=population pharmacokinetic(s)

Source: poppk-02-er-report-for-selpercatinib-in-nsclc-patients, Page 47

Figure 19.2. pcVPC for the PPK Model on the Logarithmic Scale



Source: ELIL-PMX-SELPERCATINIB- 5424_VPC_Final.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: CI=confidence interval; N=number of simulations; pcVPC=prediction-corrected visual predictive check; PPK=population pharmacokinetic(s)

Source: poppk-02-er-report-for-selpercatinib-in-nsclc-patients, Page 49

Conclusions

The PK of selpercatinib from studies LOXO-RET-17001, J2G-GH-JZJK, and J2G-MC-JZJC were described using an updated population PK model. The final model was similar to the previously developed adult model, which identified weight, dose, race, MTC tumor type and other tumor type as important covariates.

19.4.2. Exposure-Response Analysis

19.4.2.1. ER (efficacy) Executive Summary

The FDA's Assessment:

For the E-R analysis of ORR for participants with RET fusion-positive NSCLC, observations were as follows:

- The probability that a participant responds to selpercatinib (complete response or partial response) increases with higher selpercatinib exposures.

- Prior radiotherapy led to a lower possibility of response.
- No selpercatinib exposure metric was significantly associated with survival probability in the E-R analysis for PFS in participants with NSCLC.

19.4.2.2. ER (efficacy) Assessment Summary

The Applicant's Position:

A population PK and exposure-response analyses for efficacy based on LIBRETTO-431 data will be conducted and provided as supportive information within 3 months of the sNDA submission date as agreed with FDA.

19.4.2.3. ER (safety) Executive Summary

The FDA's Assessment:

The risk of increased ALT, increased AST, hypertension, or hypersensitivity did not increase with higher selpercatinib exposure for all participants and for participants with NSCLC.

In the overall population, participants with a dose reduction had higher risk of all AEs. However, this may be due to the dose reductions when AEs occurred. $AUC_{0\text{-}24h}$ was identified as the predictor with lowest AIC value for all these adverse reactions. The risk of hypertension was higher in participants older than 59 years, whereas the risk was lower in participants younger than 59 years. A higher proportion of Asian participants developed increased ALT, increased AST and hypersensitivity compared with non-Asian participants. Due to the low incidence (15 out 953 participants) and uneven distribution (11 out of 15 Asian) of hypersensitivity among the participants, the results of the analysis for hypersensitivity should be viewed with caution.

For NSCLC, participants with a dose reduction had a higher risk of increased ALT, increased AST, and hypersensitivity. $AUC_{0\text{-}24h}$ was the predictor for ALT, AST, and hypersensitivity AEs. No predictors were identified for the AE of hypertension. A higher proportion of Asian participants developed increased ALT, increased AST and hypersensitivity compared with non-Asian participants. However, as only 11 (2.2%, 9 out of 11 were Asian) participants reported hypersensitivity, the results of the analysis of hypersensitivity should be interpreted with caution.

19.4.2.4. ER (safety) Assessment Summary

The Applicant's Position:

A population PK and exposure-response analyses for safety based on LIBRETTO-431 data will be conducted and provided as supportive information within 3 months of the sNDA submission date as agreed with FDA.

The FDA's Assessment:

See 19.4.2.6 for reviewer's analysis.

19.4.2.5. ER Review Issues

Not applicable.

19.4.2.6. Reviewer's Independent Analysis

Efficacy Analysis

The efficacy E-R analysis was conducted for participants with NSCLC only from Studies J2G-MC-JZJC (selpercatinib arm) and LOXO-RET-17001. Data from Study J2G-GH-JZJK were not included in this analysis.

A total of 502 participants with RET fusion NSCLC were included in the efficacy E-R analysis for overall response rate (ORR). A summary of the demographic information and model predictors is shown in Table 6, stratified by responder status. The ORR was modeled using the individual responder status for each participant included in the analysis. The overall ORR for the participants included in this analysis was 69%.

A total of 504 participants with RET fusion NSCLC were included in the efficacy E-R analysis for PFS. A summary of the demographic information and model predictors is shown in Table 7. Overall, there were 254 events of disease progression or death.

Table 19.6. Summary of Predictors, Stratified by Response Status – ORR

	Nonresponder (N=154)	Responder (N=348)	Overall (N=502)
N			
J2G-MC-JZJC (selpercatinib arm)	22	128	150
LOXO-RET-17001	132	220	352
Sex			
Female	85 (55.2%)	197 (56.6%)	282 (56.2%)
Male	69 (44.8%)	151 (43.4%)	220 (43.8%)
Race			
White	71 (46.1%)	148 (42.5%)	219 (43.6%)
Asian	72 (46.8%)	172 (49.4%)	244 (48.6%)
Other	11 (7.1%)	28 (8.0%)	39 (7.8%)
Prior cancer radiotherapy			
No	70 (45.5%)	231 (66.4%)	301 (60.0%)
Yes	84 (54.5%)	117 (33.6%)	201 (40.0%)
Prior cancer surgery			
No	86 (55.8%)	243 (69.8%)	329 (65.5%)
Yes	68 (44.2%)	105 (30.2%)	173 (34.5%)
ECOG status at baseline			
0	50 (32.5%)	136 (39.1%)	186 (37.1%)
1	99 (64.3%)	201 (57.8%)	300 (59.8%)
2	5 (3.2%)	11 (3.2%)	16 (3.2%)
Age (years)			
Mean (SD)	60.3 (11.5)	59.3 (11.9)	59.6 (11.8)
Median [Min, Max]	59.5 [35.0, 87.0]	61.0 [23.0, 92.0]	61.0 [23.0, 92.0]

	Nonresponder (N=154)	Responder (N=348)	Overall (N=502)
Body weight (kg)			
Mean (SD)	68.1 (17.5)	67.8 (16.4)	67.9 (16.7)
Median [Min, Max]	63.5 [38.9, 122]	64.6 [40.8, 148]	64.1 [38.9, 148]
AUC24 (ng•h/mL)			
Mean (SD)	38300 (24300)	56300 (30900)	50800 (30200)
Median [Min, Max]	33300 [2540, 176000]	52000 [3000, 212000]	45800 [2540, 212000]
Cmin (ng/mL)			
Mean (SD)	1330 (840)	1870 (1160)	1700 (1100)
Median [Min, Max]	1140 [82.5, 6210]	1660 [87.3, 8510]	1460 [82.5, 8510]
Cmax (ng/mL)			
Mean (SD)	2240 (1230)	3040 (1420)	2800 (1420)
Median [Min, Max]	2010 [144, 8810]	3010 [226, 9880]	2600 [144, 9880]
AUC24_10 dose average (ng•h/mL)			
Mean (SD)	46200 (25500)	58100 (32000)	54500 (30600)
Median [Min, Max]	40200 [3820, 148000]	55700 [3040, 218000]	50300 [3040, 218000]
Cmin_10 dose average (ng/mL)			
Mean (SD)	1290 (825)	1640 (1090)	1530 (1030)
Median [Min, Max]	1160 [76.9, 5020]	1480 [30.6, 7500]	1350 [30.6, 7500]
Cmax_10 dose average (ng/mL)			
Mean (SD)	2670 (1270)	3100 (1470)	2970 (1420)
Median [Min, Max]	2440 [201, 8360]	3040 [225, 10200]	2820 [201, 10200]
Dose (mg)			
20	3 (1.9%)	4 (1.1%)	7 (1.4%)
40	7 (4.5%)	16 (4.6%)	23 (4.6%)
60	2 (1.3%)	6 (1.7%)	8 (1.6%)
80	26 (16.9%)	29 (8.3%)	55 (11.0%)
120	32 (20.8%)	38 (10.9%)	70 (13.9%)
160	84 (54.5%)	254 (73.0%)	338 (67.3%)
240	0 (0%)	1 (0.3%)	1 (0.2%)

Source: ELIL-PMX-SELPERCATINIB-5424_ORR.Rmd
Abbreviations: AUC24=area under the plasma concentration-time curve over 24 hours at steady state; AUC24_10=AUC24 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=Cmax 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=Cmin 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; ORR=overall response rate
Note: Values are presented as n (%) for categorical variables and mean (standard deviation) and median [Min, Max] for continuous variables.

Source: poppk-02-er-report-for-selpercatinib-in-nsclc-patients, Page 32

Table 19.7. Summary of Predictors, Stratified by Response Status – PFS

	Censor (N=250)	Event (N=254)	Overall (N=504)
N			
J2G-MC-JZJC (Selpercatinib Arm)	92	58	150
LOXO-RET-17001	158	196	354
Sex			
Female	132 (52.8%)	152 (59.8%)	284 (56.3%)
Male	118 (47.2%)	102 (40.2%)	220 (43.7%)
Race			
White	106 (42.4%)	115 (45.3%)	221 (43.8%)
Asian	128 (51.2%)	116 (45.7%)	244 (48.4%)
Other	16 (6.4%)	23 (9.1%)	39 (7.7%)
Prior cancer radiotherapy			
No	168 (67.2%)	134 (52.8%)	302 (59.9%)
Yes	82 (32.8%)	120 (47.2%)	202 (40.1%)
Prior cancer surgery			
No	161 (64.4%)	170 (66.9%)	331 (65.7%)
Yes	89 (35.6%)	84 (33.1%)	173 (34.3%)
ECOG status at baseline			
0	111 (44.4%)	76 (29.9%)	187 (37.1%)
1	137 (54.8%)	164 (64.6%)	301 (59.7%)
2	2 (0.8%)	14 (5.5%)	16 (3.2%)
Age (years)			
Mean (SD)	59.5 (11.4)	59.6 (12.2)	59.5 (11.8)
Median [Min, Max]	60.0 [23.0, 86.0]	61.0 [23.0, 92.0]	61.0 [23.0, 92.0]
Body weight (kg)			
Mean (SD)	68.3 (16.3)	67.4 (17.2)	67.9 (16.7)
Median [Min, Max]	64.7 [42.0, 136]	63.6 [38.9, 148]	64.1 [38.9, 148]
AUC24 (ng•h/mL)			
Mean (SD)	39200 (21000)	45300 (26700)	42300 (24200)
Median [Min, Max]	35500 [6200, 134000]	38000 [2540, 176000]	36400 [2540, 176000]
Cmin (ng/mL)			
Mean (SD)	1410 (777)	1560 (978)	1480 (887)
Median [Min, Max]	1240 [146, 5020]	1320 [97.6, 6210]	1280 [97.6, 6210]
Cmax (ng/mL)			
Mean (SD)	2290 (1010)	2590 (1360)	2440 (1210)
Median [Min, Max]	2140 [408, 6190]	2330 [144, 9750]	2230 [144, 9750]

	Censor (N=250)	Event (N=254)	Overall (N=504)
AUC24_10 dose average (ng•h/mL)			
Mean (SD)	50600 (25900)	51200 (28100)	50900 (27000)
Median [Min, Max]	48000 [3210, 148000]	45000 [3820, 218000]	46100 [3210, 218000]
Cmin_10 dose average (ng/mL)			
Mean (SD)	1430 (857)	1420 (943)	1420 (900)
Median [Min, Max]	1270 [46.2, 5020]	1170 [30.6, 7370]	1210 [30.6, 7370]
Cmax_10 dose average (ng/mL)			
Mean (SD)	2790 (1190)	2810 (1330)	2800 (1260)
Median [Min, Max]	2680 [570, 6940]	2550 [201, 10200]	2610 [201, 10200]
Dose (mg)			
20	0 (0%)	2 (0.8%)	2 (0.4%)
40	14 (5.6%)	6 (2.4%)	20 (4.0%)
60	0 (0%)	3 (1.2%)	3 (0.6%)
80	38 (15.2%)	39 (15.4%)	77 (15.3%)
120	62 (24.8%)	52 (20.5%)	114 (22.6%)
160	136 (54.4%)	152 (59.8%)	288 (57.1%)

Source: ELIL-PMX-SELPERCATINIB-5424_PFS.Rmd

Abbreviations: AUC24=area under the plasma concentration-time curve over 24 hours at steady state; AUC24_10=AUC24 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=Cmax 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=Cmin 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; PFS=progression-free survival

Note: Values are presented as n (%) for categorical variables and mean (standard deviation) and median [Min, Max] for continuous variables.

Source: poppk-02-er-report-for-selpercatinib-in-nsclc-patients, Page 34

Efficacy endpoint: ORR

The final E-R model for ORR included $AUC_{0\text{-}24h}$ and prior radiation therapy as predictors of response. The odds ratio for participants who received prior radiation therapy in reference to those who did not (95% CI) was 0.49 (0.3, 0.7). The odds ratio increases with increased $AUC_{0\text{-}24h}$ and even at the 5th $AUC_{0\text{-}24h}$ percentile (13255 ng•h/mL), the odds ratio was 1.4 (1.2, 1.6).

Reviewer comments:

Based on the Applicant's proposed dataset require by IR and R codes, the odds ratio for participants who received prior radiation therapy in reference to those who did not (95% CI) was 0.44 (0.27, 0.61). The odds ratios at the 5th $AUC_{0\text{-}24h}$ percentile and 95th $AUC_{0\text{-}24h}$ percentile were 1.4 and 11.1. These ORR ratios are similar to those proposed by Applicants.

Efficacy endpoint: PFS

An exploratory analysis of survival probability by exposure metrics ($AUC_{0\text{-}24h}$, $AUC_{0\text{-}24h}$ 10, Cmax, Cmax_10, Cmin, Cmin_10) was conducted using KM plots. None of the exposure metrics

showed a significant relationship with survival probability. Therefore, no further E-R modeling of PFS was pursued.

Reviewer comments:

The P value in KM plots for PFS and Cmax_10 is 0.036, which is different from Applicants' evaluation report (p value: 0.092). However, survival probability is NOT significant related to exposure. Therefore, the Applicant's analysis is acceptable.

Safety E-R Data

Two safety E-R analyses were conducted. One analysis included all participants (overall safety) from Studies J2G-MC-JZJC (selpercatinib arm only) and LOXO-RET-17001, and the other analysis included participants with NSCLC only. Data from Study J2G-GH-JZJK were not included in these analyses.

A total of 953 participants were included in the overall safety E-R analysis whereas a total 504 participants were included in the safety E-R analysis for NSCLC participants only. The incidence rates for all participants were 14% (131 of 953 participants) for increased ALT, 10% (93 of 953 participants) for increased AST, 20% (190 of 953 participants) for hypertension, and 1.6% (15 of 953 participants) for hypersensitivity. The incidence rates for participants with NSCLC for were 18% (88 of 504 participants) for increased ALT, 11% (57 of 504 participants) for increased AST, 20% (100 of 504 participants) for hypertension, and 2.2% (11 of 504 participants) for hypersensitivity.

Safety endpoint: ALT

The ER final model included selpercatinib exposure, dose reduction status, and race as predictors of time-to-first increased ALT. The lowest selpercatinib $AUC_{0\text{-}24h}$ quartile appeared to have the highest proportion of participants with increased ALT compared with the other 3 selpercatinib $AUC_{0\text{-}24h}$ quartiles, and a higher proportion of participants with a dose reduction had increased ALT compared with participants without a dose reduction. A higher proportion of Asian participants had increased ALT compared with non-Asian participants. Overall, participants with a dose reduction had a hazard ratio (95% CI) of 6.8 (4.4, 10.5) relative to participants without a dose reduction. Additionally, Asian participants had a hazard ratio (95% CI) of 2.5 (1.8, 3.5) relative to non-Asian participants.

Meanwhile, for NSCLC, participants with a dose reduction had a hazard ratio (95% CI) of 7.4 (4.2, 12.9) relative to participants without a dose reduction. Additionally, Asian participants had a hazard ratio (95% CI) of 1.9 (1.2, 2.9) relative to non-Asian participants.

Safety endpoint: AST

The ER final model included selpercatinib exposure, dose reduction status, and race as predictors of time-to-first increased AST. The lowest selpercatinib $AUC_{0\text{-}24h}$ quartile appeared to have the highest proportion of participants with increased AST compared with the other 3 selpercatinib quartiles, and a higher proportion of participants with a dose reduction had increased AST compared with participants without a dose reduction. A higher proportion of Asian participants

had increased AST compared with non-Asian participants. Overall, participants with a dose reduction had a hazard ratio (95% CI) of 5.7 (3.5, 9.4) relative to participants without a dose reduction. Additionally, Asian participants had a hazard ratio (95% CI) of 2.9 (1.9, 4.3) relative to non-Asian participants.

Meanwhile, for NSCLC, participants with a dose reduction had a hazard ratio (95% CI) of 5.5 (2.8, 10) relative to participants without a dose reduction. Additionally, Asian participants had a hazard ratio (95% CI) of 3 (1.7, 5.3) relative to non-Asian participants.

Safety endpoint: Hypertension

The ER final model included selpercatinib exposure, dose reduction status, and age as predictors of time-to-first hypertension. Overall, participants 34 years of age had a hazard ratio (95% CI) of 0.7 (0.5, 0.9) relative to participants 59 years of age. On the other hand, participants 78 years of age had a hazard ratio (95% CI) of 1.4 (1.1, 1.7) relative to participants 59 years of age. Participants with a dose reduction had a hazard ratio (95% CI) of 1.4 (1.1, 1.9) relative to participants without a dose reduction.

Meanwhile, for NSCLC, no predictor was identified as a significant predictor of time-to-first hypertension ($p>0.05$).

Safety endpoint: Hypersensitivity

The ER final model included selpercatinib exposure, dose reduction status, and race as predictors of time-to-first hypersensitivity. Overall, participants with a dose reduction relative to participants without a dose reduction had a hazard ratio (95% CI) of 9.6 (2.0, 45) for all participants. Due to the low incidence of the hypersensitivity (15 out of 953 participants had hypersensitivity AE) and the uneven race distribution among participants who had the AE (11 out of 15 participants were Asian), the analysis results should be interpreted with caution.

Meanwhile, for NSCLC, participants with a dose reduction had a hazard ratio (95% CI) of 14 (1.6, 116) relative to participants without a dose reduction. Additionally, Asian participants had a hazard ratio (95% CI) of 6.0 (1.2, 29) relative to non-Asian participants. The analysis results should be interpreted with caution, as only 11 (2.2%) of participants with NSCLC reported hypersensitivity (9 out of 11 were Asian).

CONCLUSIONS

• An updated PPK model was developed, and the pcVPCs showed a good agreement between the observed and predicted concentrations, indicating that the model adequately describes selpercatinib exposure in all included participants. The updated model included tumor type as a covariate on CL/F. However, there is a significant overlap in exposure metrics across all 3 tumor types suggesting the impact of tumor type on CL/F is not clinically significant.

• For the efficacy E-R analysis of ORR for participants with RET fusion-positive NSCLC, observations were as follows:

-The probability that a participant is a responder (complete response or partial response) increased with increasing selpercatinib exposures.

-Prior radio therapy led to a lower possibility of response.

• No selpercatinib exposure metric was identified to be significantly associated with survival probability in the efficacy E-R analysis for PFS in participants with NSCLC.

• Increased ALT, increased AST, hypertension, and hypersensitivity showed no increased risk with higher selpercatinib exposure for all participants and for participants with NSCLC.

- In the overall population, participants with a dose reduction had higher risk of all AEs. However, this may be due to the dose reductions when AEs occurred. $AUC_{0\text{-}24h}$ was the predictor for all 4 AEs of interest. For hypertension, the risk of the AE is higher in participants older than 59 years, whereas the risk was lower in participants younger than 59 years. A higher proportion of Asian participants was found with increased ALT, increased AST and hypersensitivity compared with non-Asian participants. Due to the low incidence (15 out 953 participant) and uneven distribution (11 out of 15 were Asian) of hypersensitivity among the participants, the analysis results for hypersensitivity should be viewed with caution.

- For NSCLC, participants with a dose reduction had a higher risk of increased ALT, increased AST, and hypersensitivity. $AUC_{0\text{-}24h}$ was the predictor for ALT, AST, and hypersensitivity AEs. No predictors were identified for hypertension. A higher proportion of Asian participants developed increased ALT, increased AST and hypersensitivity compared with non-Asian participants. However, as only 11 (2.2%, 9 out of 11 were Asian) participants reported hypersensitivity in participants with NSCLC, the results of the analysis of hypersensitivity should be interpreted with caution.

19.4.2.7. Overall benefit-risk evaluation based on ER analyses

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

Not applicable

NDA 213246 S-011/NDA 218160 S-003				
Signatures				
DISCIPLINE	**REVIEWER**	**OFFICE/DIVISION**	**SECTIONS AUTHORED/ APPROVED**	**AUTHORED/ APPROVED**
Clinical Reviewer	Elizabeth Duke, MD	OOD/DO2	Sections: 1-4, 7-13	**Select one:** ☒Authored ☐Approved
	Signature: ELIZABETH S. DUKE -S Digitally signed by ELIZABETH S. DUKE -S Date: 2024.09.24 12:17:03 -04'00'			
Statistical Reviewer	Arup Sinha, PhD	OB/DBV	Sections: 1, 8	**Select one:** ☒Authored ☐Approved
	Signature: Arup K. Sinha -S Digitally signed by Arup K. Sinha -S Date: 2024.09.24 13:03:09 -04'00'			
Statistical Team Leader	Xiaoxue Li, PhD	OB/DBV	Sections: 1, 8	**Select one:** ☒Authored ☒Approved
	Signature: Xiaoxue Li -S Digitally signed by Xiaoxue Li -S Date: 2024.09.24 12:24:41 -04'00'			
Deputy Division Director (OB)	Pallavi Mishra-Kalyani, PhD	OB/DBV	Sections: 1, 8	**Select one:** ☒Approved
	Signature: Pallavi S. Mishra-kalyani -S Digitally signed by Pallavi S. Mishra-kalyani -S Date: 2024.09.25 09:07:45 -04'00'			
Associate Director for Labeling (ADL)	Barbara Scepura	OND/OOD	Sections:11	**Select one:** ☐Authored ☐Approved
	Signature: Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S Date: 2024.09.25 15:31:13 -04'00'			
Clinical Pharmacology Reviewer	Miao Zhao PhD	OCP/DCP I	Sections: 6, 19	**Select one:** ☒Authored ☐Approved
	Signature: see signature in DARRTs Miao Zhao -S Digitally signed by Miao Zhao -S Date: 2024.09.25 13:13:29 -04'00'			
Clinical Pharmacology Team Leader	Jeanne Fourie Zirkelbach, PhD	OCP/DCP II	Sections: 6, 19	**Select one:** ☐Authored ☒Approved
	Signature: see signature in DARRTs Jeanne Fourie Zirkelbach -S Digitally signed by Jeanne Fourie Zirkelbach -S Date: 2024.09.25 12:36:04 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Deputy Division Director	Stacy Shord PharmD	OCP/DCP II	Sections: 6, 19	**Select one:** ☐Authored ☒Approved
	Signature: Stacy Shord -S Digitally signed by Stacy Shord -S Date: 2024.09.24 12:41:20 -04'00'			
Pharmacometrics Team Leader	Youwei Bi, PhD	OCP/DPM	Sections: 6, 19	**Select one:** ☐Authored ☒Approved
	Signature: Youwei Bi -S Digitally signed by Youwei Bi -S Date: 2024.09.24 12:31:19 -04'00'			
Pharmacometrics Reviewer	Hezhen Wang, PhD	OCP/DPM	Sections: 6, 19	**Select one:** ☒Authored ☐Approved
	Signature: Hezhen Wang -S Digitally signed by Hezhen Wang -S Date: 2024.09.24 13:40:46 -04'00'			
Clinical/Cross-Disciplinary Team Lead	Diana Bradford, MD	OOD/DO2	Sections: ALL	**Select one:** ☒Authored ☒Approved
	Signature: See DARRTS electronic signature			
Deputy Division Director (Clinical)	Nicole Drezner, MD	OOD/DO2	Sections: ALL	☒Authored ☒Approved
	Signature: See DARRTS electronic signature			

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DIANA L BRADFORD
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09/26/2024 10:45:08 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213246Orig1s011

PRODUCT QUALITY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number:** NDA-213246-SUPPL-011
   sNDA Recommendation: Approval
   sNDA Managed by: OND

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	PA	11/28/2023	11/29/2023	12/13/2023	05/29/2024	04/18/2024

3. **Provides For:**
   - to include interim efficacy and safety results of LIBRETTO-431 study in the US Product Insert (USPI).

4. **Review #**: 01

5. **Clinical Review Division**: DO2

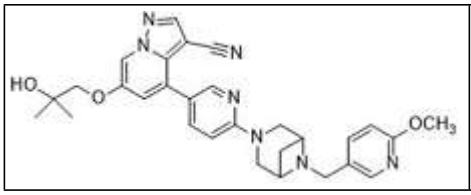
6. **Name and Address of Applicant**:
   Eli Lilly and Company
   Lilly Corporate Center
   Indianapolis, IN, USA 46285

   Contact: Viktoriya Ilaria
   Phone: (201) 213-9104
   Email: ilaria_viktoriya@lilly.com

7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product	Orphan Designation
RETEVMO™ (selpercatinib)	Capsules	40 mg and 80 mg	Oral	Rx	Yes	18-6752

8. **Chemical Name and Structure of Drug Substance**:



USAN: selpercatinib
Chemical name: 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
Molecular formula: $C_{29}H_{31}N_7O_3$
MW: 525.61 g/mol

9. **Indication**:

- for the treatment of adult patients with advanced or metastatic RET fusion-positive solid tumors with disease progression on or after prior systemic therapies or who have no satisfactory therapeutic options.

10. Supporting/Relating Documents: None

11. Consults: None

12. Executive Summary:

Lilly is submitting this supplement to NDA 213246 proposing to include interim efficacy and safety results of LIBRETTO-431 study in the US Product Insert (USPI). The supplement is submitted as labeling supplement but is converted to efficacy supplement.

The applicant has claimed categorical exclusion from the determination of an environmental assessment under 21 CFR Part 25.31 (b). The total US annual peak sales volume of selpercatinib will be less than (b) (4) considering both the currently approved indications of therapeutic regimens and the indication in the supplement. Assuming that a daily discharge of water to sewage treatment facilities in the United States is about 1.26×10^{11} liters (US EPA 2016), a maximum expected introduction concentration of selpercatinib at the point of entry to the environment (EIC) will be less than (b) (4) µg/L. Since the EIC is below 1 part per billion (1 µg/L), a categorical exclusion is deemed appropriate by 21 CFR 25.31 (b). To the applicant's knowledge, no extraordinary circumstances exist in accordance with 21 CFR sections 25.15(a) and 21. Therefore, the request for categorical exclusion may be granted.

The supplement provides updated PI. There are no proposed CMC related changes to sections 2, 3, 11 and 16.

The changes proposed in S011 are acceptable from a CMC standpoint.

13. Conclusions & Recommendations: This supplement is recommended for approval.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:

Qi Liu, Ph.D., CMC reviewer, Branch 1, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:

Rohit Kolhatkar, Ph.D., SPQA, Branch 1, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

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/s/

QI LIU
05/08/2024 01:28:25 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213246Orig1s011

OTHER REVIEW(S)

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

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

Memorandum

Date: September 18, 2024

To: Tselaine Jones Smith, Consumer Safety Officer, 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 and RETEVMO® (selpercatinib) tablets, for oral use

NDA: 218160; 213246 S-011

Background:

In response to DO2's consult request dated December 19, 2023, OPDP has reviewed the proposed Prescribing Information (PI) for supplement S-011 for RETEVMO® (selpercatanib) capsules, for oral use and RETEVMO® (selpercatinib) tablets, for oral use. This labeling supplement proposes to update the current prescribing information to include interim efficacy and safety results from LIBRETTO-431. LIBRETTO-431 study, is a global, multicenter, randomized, open-label, Phase 3 study comparing selpercatinib to pemetrexed platinum-based therapy with or without pembrolizumab in patients with unresectable locally advanced or metastatic RET fusion-positive NSCLC.

PI:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on September 5, 2024, and our comments are provided below.

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
14 CLINICAL STUDIES: LIBRETTO 431	*"*Overall survival may be affected by the imbalance in post-progression therapies*."*	OPDP is concerned that this information will be used in promotion to suggest that this OS detriment is due to the imbalance in post-progression therapies, rather than being reflective of treatment with Retevmo and therefore minimize any concerns that may arise due to the HR crossing 1. Furthermore, we are concerned with the inclusion in the PI of a conclusion like this based on interim data. Unless the review division believes that this is truly a statistically supportable claim which is necessary for interpreting the data and is necessary for the safe and effective use of the drug, we recommend deleting this statement.

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