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 and BCRP 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: 12/2024

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

Current RETEVMO Dosage	Recommended 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

Laboratory Abnormality	RETEVMO[1]	
	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

Laboratory Abnormality	RETEVMO[1]		Cabozantinib or Vandetanib[1]	
	Grades 1-4[#] %	Grades 3-4 %	Grades 1-4[#] %	Grades 3-4 %
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 and BCRP Substrates

RETEVMO is a P-gp and BCRP inhibitor. Concomitant use of RETEVMO with P-gp or BCRP 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 or BCRP substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for P-gp and BCRP 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

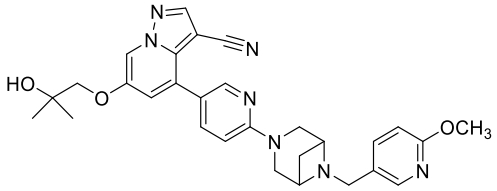
Reduce the dose when administering RETEVMO to patients with severe [total bilirubin greater than 3 to 10 times upper limit of normal (ULN) and any AST] hepatic impairment *[see Dosage and Administration (2.7)]*.

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_{0-24h} 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 1.1-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), 1.3-fold in subjects with moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST), and 1.8-fold in subjects with severe (total bilirubin greater than 3 to 10 times ULN and any AST) hepatic impairment, 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 $AUC_{0\text{-}INF}$ 2.3-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 2-fold and C_{max} 1.5 to 1.8-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 $AUC_{0\text{-}INF}$ 2.9-fold and C_{max} 1.9-fold.

CYP3A Substrates: Coadministration of RETEVMO with midazolam (sensitive CYP3A substrate) increased the midazolam $AUC_{0\text{-}INF}$ 1.5-fold and C_{max} 1.4-fold.

P-glycoprotein (P-gp) Substrates: Coadministration of RETEVMO with dabigatran (P-gp substrate) increased the dabigatran $AUC_{0\text{-}INF}$ 1.4-fold and C_{max} 1.4-fold.

BCRP Substrates: Coadministration of RETEVMO with rosuvastatin (BCRP substrate) increased the rosuvastatin $AUC_{0\text{-}INF}$ by 1.9-fold and C_{max} by 1.7-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. Selpercatinib may increase serum creatinine by decreasing renal tubular secretion of creatinine via inhibition of MATE1 *[see Adverse Reactions (6.1)]*.

Selpercatinib does not inhibit OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BSEP, and MATE2-K at clinically relevant concentrations.

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 mg 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

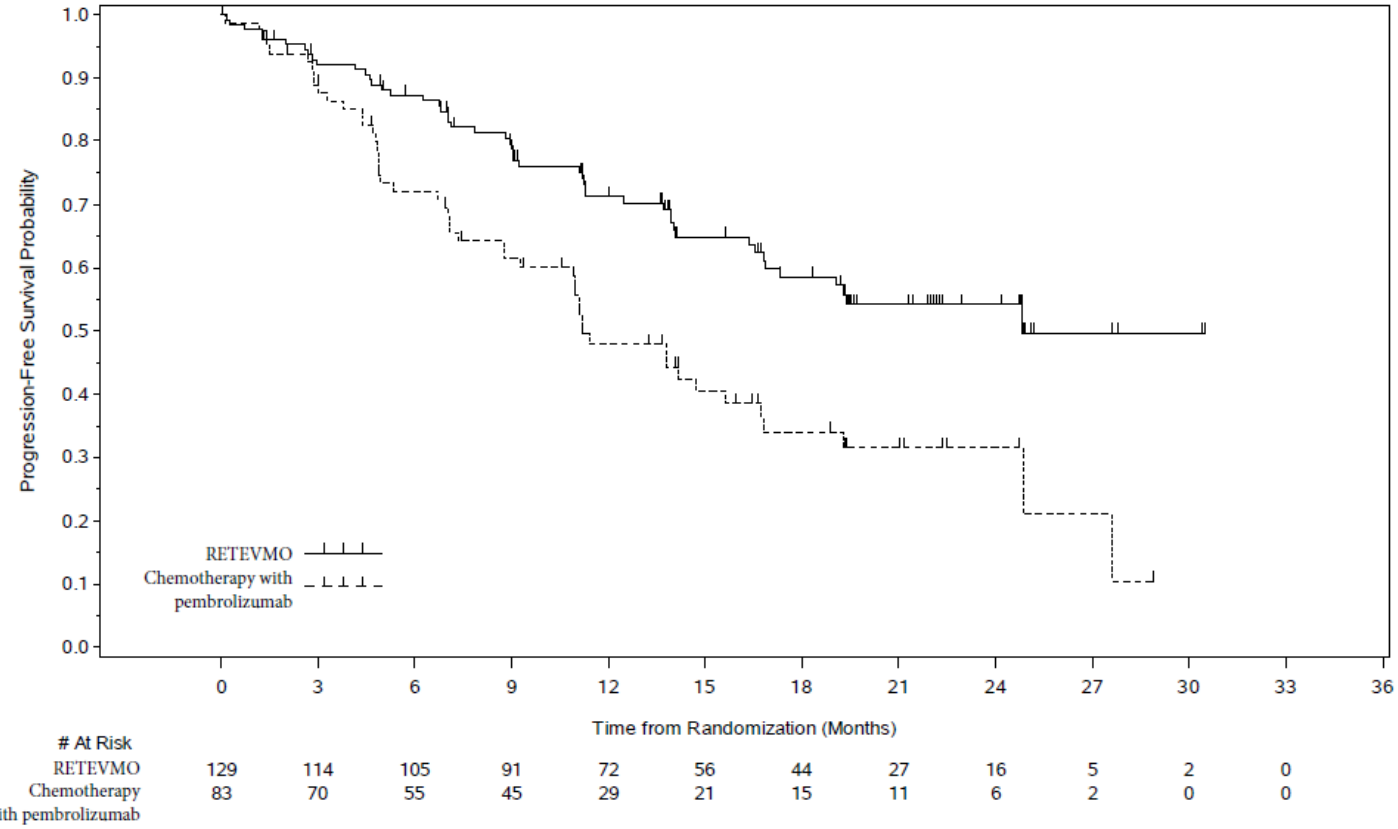


Figure 1: Kaplan-Meier Curves of Progression-Free Survival in LIBRETTO-431: RETEVMO versus Chemotherapy with Pembrolizumab

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

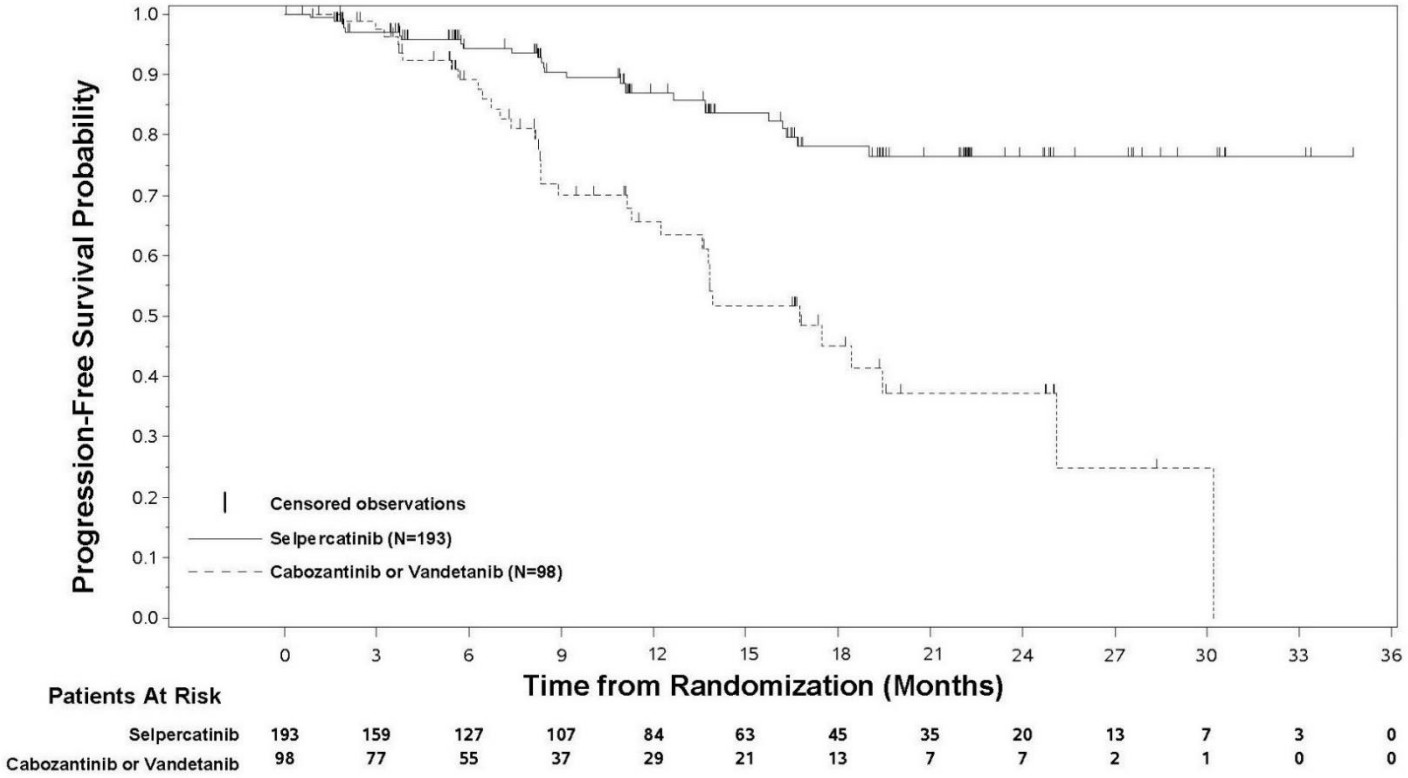


Figure 2: Kaplan-Meier Curves of Progression-Free Survival in LIBRETTO-531: RETEVMO versus Cabozantinib or Vandetanib

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 ≤25% of time	 61% 90%	 30% 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)]*.

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