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 (1.2, 1.3, 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] (1.2)
- Adult and pediatric patients 2 years of age and older with advanced or metastatic thyroid cancer with a *RET* gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate) (1.3)
- Adult and pediatric patients 2 years of age and older with locally advanced or metastatic solid tumors with a *RET* gene fusion, as detected by an FDA-approved test, that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options[1] (1.4)

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

----------DOSAGE AND ADMINISTRATION----------

- Select patients for treatment with RETEVMO based on the presence of a *RET* gene fusion (NSCLC, thyroid, or other solid tumors) or specific *RET* gene mutation (MTC). (2.1, 14)
- Adult and adolescent patients 12 years of age or older:

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

  the recommended dosage is based on body surface area (2.3):
  - 0.33 to 0.65 m^2: 40 mg orally three times daily
  - 0.66 to 1.08 m^2: 80 mg orally twice daily
  - 1.09 to 1.52 m^2: 120 mg orally twice daily
  - ≥1.53 m^2: 160 mg orally twice daily
- Reduce RETEVMO dose in patients with severe hepatic impairment. (2.7, 8.7)

----------DOSAGE FORMS AND STRENGTHS----------

- Capsules: 40 mg, 80 mg. (3)
- Tablets: 40 mg, 80 mg, 120 mg, 160 mg. (3)

---------- CONTRAINDICATIONS ----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- *Hepatotoxicity:* Monitor ALT and AST prior to initiating RETEVMO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce the dose, or permanently discontinue RETEVMO based on severity. (2.5, 5.1)
- *Interstitial Lung Disease (ILD)/Pneumonitis*: Monitor for new or worsening pulmonary symptoms. Withhold, reduce the dose or permanently discontinue RETEVMO based on severity. (2.5, 5.2)
- *Hypertension:* Do not initiate RETEVMO in patients with uncontrolled hypertension. Optimize blood pressure (BP) prior to initiating RETEVMO. Monitor BP after 1 week, at least monthly thereafter and as clinically indicated. Withhold, reduce the dose, or permanently discontinue RETEVMO based on severity. (2.5, 5.3)
- *QT Interval Prolongation:* Monitor patients who are at significant risk of developing QTc prolongation. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment. Monitor QT interval more frequently when RETEVMO is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and reduce the dose or permanently discontinue RETEVMO based on severity. (2.5, 5.4)
- *Hemorrhagic Events:* Permanently discontinue RETEVMO in patients with severe or life-threatening hemorrhage. (2.5, 5.5)
- *Hypersensitivity:* Withhold RETEVMO and initiate corticosteroids. Upon resolution, resume at a reduced dose and increase dose by 1 dose level each week until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. (2.5, 5.6)
- *Tumor Lysis Syndrome:* Closely monitor patients at risk and treat as clinically indicated. (5.7)
- *Risk of Impaired Wound Healing:* Withhold RETEVMO for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of RETEVMO after resolution of wound healing complications has not been established. (5.8)
- *Hypothyroidism:* Monitor thyroid function before treatment with RETEVMO and periodically during treatment. Withhold until clinically stable or permanently discontinue based on severity. (5.9)
- *Embryo-Fetal Toxicity:* Can cause fetal harm. Advise females of reproductive potential of the possible risk to a fetus and to use effective contraception. (5.10, 8.1, 8.3)
- *Slipped Capital Femoral Epiphysis/Slipped Upper Femoral Epiphysis (SCFE/SUFE) in Pediatric Patients:* Monitor patients for symptoms indicative of SCFE/SUFE and treat as medically and surgically appropriate (5.11, 6.1)

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

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

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

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

- Adult patients with solid tumors: decreased lymphocytes, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), decreased sodium, and decreased calcium. (6)
- Pediatric patients with solid tumors: decreased calcium, decreased hemoglobin, and decreased neutrophils. (6)

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

---------- DRUG INTERACTIONS ----------

- *Acid-Reducing Agents:* Avoid coadministration. If coadministration cannot be avoided, take RETEVMO with food (with PPI) or modify its administration time (with H2 receptor antagonist or locally-acting antacid). (2.4, 7.1)
- *Strong and Moderate CYP3A Inhibitors:* Avoid coadministration. If coadministration cannot be avoided, reduce the RETEVMO dose. (2.6, 7.1)
- *Strong and Moderate CYP3A Inducers:* Avoid coadministration. (7.1)

- *CYP2C8 and CYP3A Substrates:* Avoid coadministration. If coadministration cannot be avoided, modify the substrate dosage as recommended in its product labeling. (7.2)
- *Certain P-gp Substrates:* Avoid coadministration. If coadministration cannot be avoided, modify the substrate dosage as recommended in its product labeling. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

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

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

Revised:06/2024

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.

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

1.3 *RET* Fusion-Positive Thyroid Cancer

RETEVMO is indicated for the treatment of adult and pediatric patients 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

	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 *[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.

RET Gene Fusion or Gene Mutation Positive Solid Tumors

LIBRETTO-001

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

The median age was 59 years (range: 15 to 92 years); 0.3% were pediatric patients 12 to 16 years of age; 51% were male; and 69% were White, 23% were Asian, 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.

Increased Creatinine

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

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on RETEVMO

Acid-Reducing Agents

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

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

Strong and Moderate CYP3A Inhibitors

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

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

Strong and Moderate CYP3A Inducers

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

Avoid coadministration of strong or moderate CYP3A inducers with RETEVMO.

7.2 Effects of RETEVMO on Other Drugs

CYP2C8 and CYP3A Substrates

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

Certain P-gp Substrates

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

7.3 Drugs that Prolong QT Interval

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

Females

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

Males

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

Infertility

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

8.4 Pediatric Use

The safety and effectiveness of RETEVMO have been established in pediatric patients 2 years of age and older for the treatment of:

- advanced or metastatic medullary thyroid cancer (MTC) with a *RET* mutation who require systemic therapy
- advanced or metastatic thyroid cancer with a *RET* gene fusion who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate)
- locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.

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

The safety and effectiveness of RETEVMO have not been established in these indications in patients less than 2 years of age.

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

Juvenile Animal Toxicity Data

In a juvenile rat toxicity study, animals were dosed daily with selpercatinib from post-natal day 21 to day 70 (approximately equivalent to a human child to late adolescent). Selpercatinib increased physeal thickness of multiple bones, extending into the metaphysis and associated with decreased trabecular bone, which was not reversible at doses approximately equivalent to or greater than the adult human exposure at the clinical dose of 160 mg twice daily. Growth plate changes were associated with impairment of bone modeling, resulting in decreased femur length and with reduction in bone mineral density. Selpercatinib also induced reversible hypocellularity of bone marrow in males at ≥30 mg/kg (approximately equivalent to or greater than the adult human exposure at the clinical dose of 160 mg twice daily), and reversible alterations of dentin composition at ≥50 mg/kg (approximately 3 times the adult human exposure at the clinical dose of 160 mg twice daily). Irreversible, dose-dependent degeneration of testicular germinal epithelium, with vacuolation of Sertoli cells and corresponding depletion of spermatozoa in the epididymides, was also observed at ≥ 30 mg/kg (approximately equivalent to or greater than the adult human exposure at the clinical dose of 160 mg twice daily) and affected male reproductive performance at 50 mg/kg (approximately 3 times the adult human exposure at the clinical dose of 160 mg twice daily). Females exhibited delay in attainment of vaginal patency, a marker of sexual maturity, at 125 mg/kg (approximately 4 times the adult human exposure at the clinical dose of 160 mg twice daily); this affect was associated with lower mean body weight. Similar effects in irregular thickening of growth plates in adult rats and minipigs,

and tooth dysplasia and malocclusion, resulting in tooth loss in adult rats were observed in repeat dose studies of up to 13-week duration with selpercatinib.

Monitor growth plates in 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

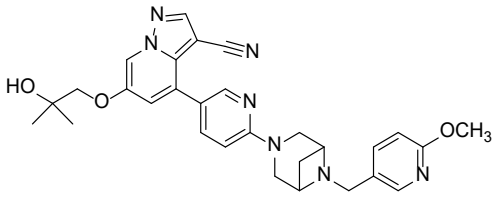
No dosage modification is recommended for patients with mild to severe renal impairment [estimated Glomerular Filtration Rate (eGFR) ≥15 to 89 mL/min, estimated by Modification of Diet in Renal Disease (MDRD) equation]. The recommended dosage has not been established for patients with end-stage renal 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 191 L.

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

Elimination

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

Metabolism

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

Excretion

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

Specific Populations

The apparent volume of distribution and clearance of selpercatinib increase with increasing body weight (9.6 kg to 179 kg).

No clinically significant differences in the pharmacokinetics of selpercatinib were observed based on age (2 years to 92 years), sex, or mild, moderate, or severe renal impairment (eGFR ≥15 to 89 mL/min). The effect of ESRD on selpercatinib pharmacokinetics has not been studied.

Pediatric patients

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

Patients with Hepatic Impairment

The selpercatinib $AUC_{0\text{-}INF}$ increased 1.07-fold, 1.32-fold, and 1.77-fold in subjects with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST), moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST), and severe (total bilirubin greater than 3 to 10 times ULN and any AST) hepatic impairment, respectively, compared to subjects with normal hepatic function.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Proton-Pump Inhibitors (PPI): Coadministration with multiple daily doses of omeprazole (PPI) decreased selpercatinib $AUC_{0\text{-}INF}$ and C_{max} when RETEVMO was administered fasting. Coadministration with multiple daily doses of omeprazole did not significantly change the selpercatinib $AUC_{0\text{-}INF}$ and C_{max} when RETEVMO was administered with food (Table 10).

Table 10: Change in Selpercatinib Exposure After Coadministration with PPI

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

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

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

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

Strong CYP3A Inhibitors: Coadministration of multiple doses of itraconazole (strong CYP3A inhibitor) increased the selpercatinib $AUC_{0\text{-}INF}$ 2.33-fold and C_{max} 1.3-fold.

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

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

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

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

CYP2C8 Substrates: Coadministration of RETEVMO with repaglinide (sensitive CYP2C8 substrate) increased the repaglinide $AUC_{0\text{-}INF}$ 2.88-fold and C_{max} 1.91-fold.

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

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

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

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

In Vitro Studies

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

14 CLINICAL STUDIES

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

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

duration of response (DOR), as determined by a blinded independent review committee (BIRC) according to RECIST v1.1.

RET Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy

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

The median age was 61 years (range: 23 to 81); 57% were female; 44% were White, 48% were Asian, 4.9% were Black 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-PD-1/PD-L1 therapy. *RET* fusions were detected in 94% of patients using NGS (84.6% tumor samples; 9.3% blood or plasma samples), 4.0% using FISH, 1.6% using PCR and 0.4% by other local testing methods.

Efficacy results for previously treated *RET* fusion-positive NSCLC are summarized in Table 11.

Table 11: 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 12.

Table 12: Efficacy Results in LIBRETTO-001 (Treatment-Naïve *RET* Fusion-Positive NSCLC)

	RETEVMO (n =69)
Overall Response Rate[1] (95% CI)	84% (73%, 92%)
Complete response	5.8%
Partial response	78%

Duration of Response	
Median in months (95% CI)	20.2 (13, NE)
% with ≥ 12 months[2]	50%

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NE = not estimable

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

14.2 *RET*-Mutant Medullary Thyroid Cancer

LIBRETTO-001

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

RET-Mutant MTC Previously Treated with Cabozantinib or Vandetanib

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

The median age was 57 years (range: 17 to 84); 66% were male; 89% were White, 1.8% were Black or African American; and 7% were Hispanic/Latino. 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 13.

Table 13: 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 14.

Table 14: Efficacy Results in LIBRETTO-001 (*RET*-Mutant MTC Previously Treated with Cabozantinib or Vandetanib)

	RETEVMO (n = 55)
Overall Response Rate[1] (95% CI)	69% (55%, 81%)

Complete response	9%
Partial response	60%
Duration of Response	
Median in months (95% CI)	NE (19.1, NE)
% with ≥6 months[2]	76

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NE = not estimable

Cabozantinib and Vandetanib-naïve *RET*-Mutant MTC

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

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

Efficacy results for cabozantinib and vandetanib-naïve *RET*-mutant MTC are summarized in Table 15.

Table 15: Efficacy Results in LIBRETTO-001 (Cabozantinib and Vandetanib-naïve *RET*-Mutant MTC)

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

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NE = not estimable

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 selpercatinib 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 16.

Table 16: 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 17.

Table 17: 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 18.

Table 18: 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 19 and Table 20.

Table 19: 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 20: Efficacy Results by Tumor Type in LIBRETTO-001 (Other *RET* Fusion-Positive Solid Tumors)

Tumor Type	Patients (n = 41)	ORR[1,2]		DOR Range (months)
		n (%)	95% CI	
Pancreatic adenocarcinoma	11	6 (55%)	(23, 83)	2.5, 38.3+
Colorectal	10	2 (20%)	(2.5, 56)	5.6, 13.3
Salivary	4	2 (50%)	(7, 93)	5.7, 28.8+
Unknown primary	3	1 (33%)	(0.8, 91)	9.2
Breast	2	PR, CR	NA	2.3+, 17.3
Sarcoma (soft tissue)	2	PR, SD	NA	14.9+
Xanthogranuloma	2	NE, NE	NA	NA
Carcinoid (bronchial)	1	PR	NA	24.1+
Carcinoma of the skin	1	NE	NA	NA
Cholangiocarcinoma	1	PR	NA	5.6+
Ovarian	1	PR	NA	14.5+
Pulmonary carcinosarcoma	1	NE	NA	NA
Rectal neuroendocrine	1	NE	NA	NA
Small intestine	1	CR	NA	24.5

+ denotes ongoing response.

1 Confirmed overall response rate assessed by BIRC.

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

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

LIBRETTO-121

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

RETEVMO capsules are supplied as follows:

Capsule Strength	Description	Package Configuration	NDC Number
40 mg	Gray opaque, imprinted with “Lilly”, “3977” and “40 mg” in black ink	60 count bottle	NDC 0002-3977-60
80 mg	Blue opaque, imprinted with “Lilly”, “2980” and “80 mg” in black ink	60 count bottle	NDC 0002-2980-60
		120 count bottle	NDC 0002-2980-26

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

Tablet Strength	Description	Package Configuration	NDC Number
40 mg	Light gray, film coated, round tablets debossed with “Ret 40” on one side and “5340” on the other side	60 count bottle	NDC 0002-5340-60

80 mg	Dark red-purple, film coated, round tablets debossed with “Ret 80” on one side and ”6082” on the other side	60 count bottle	NDC 0002-6082-60
120 mg	Light purple, film coated, round tablets debossed with “Ret 120” on one side and “6120” on the other side	60 count bottle	NDC 0002-6120-60
160 mg	Light pink, film coated, round tablets debossed with Ret “160” on one side and “5562” on the other side	60 count bottle	NDC 0002-5562-60

Storage and Handling

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

17 PATIENT COUNSELING INFORMATION

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

Hepatotoxicity

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

Interstitial Lung Disease (ILD)/Pneumonitis

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

Hypertension

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

QT Prolongation

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

Hemorrhagic Events

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

Hypersensitivity Reactions

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

Tumor Lysis Syndrome

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

Risk of Impaired Wound Healing

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

Hypothyroidism

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

Slipped Capital Femoral Epiphysis/Slipped Upper Femoral Epiphysis

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

Embryo-Fetal Toxicity

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

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

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

Lactation

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

Infertility

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

Drug Interactions

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

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

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

RET-0006-USPI-20240612

PATIENT INFORMATION

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

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

What is RETEVMO?

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

- adults with locally advanced non-small cell lung cancer (NSCLC) or NSCLC that has spread.
- adults and children 2 years of age and older with advanced medullary thyroid cancer (MTC) or MTC that has spread, who require a medicine by mouth or injection (systemic therapy).
- adults and children 2 years of age and older with advanced thyroid cancer or thyroid cancer that has spread who require a medicine by mouth or injection (systemic therapy), and who have received radioactive iodine and it did not work or is no longer working.
- adults and children 2 years of age and older with locally advanced solid tumors (cancers) or solid tumors that have spread, and have gotten worse (progressed) on or after other treatment or there are no satisfactory treatment options.

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

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

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

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

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

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

During treatment with RETEVMO, you should avoid taking:

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

If you cannot avoid taking PPIs, H2 blockers, or antacids, see "**How should I take RETEVMO?**" for more information on how to take RETEVMO with these medicines.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take RETEVMO?

- Take RETEVMO exactly as your healthcare provider tells you.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with RETEVMO if you have side effects. Do not change your dose or stop taking RETEVMO unless your healthcare provider tells you.
- Swallow RETEVMO capsules and tablets whole. Do not crush or chew.
- Do not give RETEVMO capsule to your child if they are unable to swallow a capsule.
- Take RETEVMO with or without food.
- If you take a proton-pump inhibitor (PPIs), such as dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole sodium, and rabeprazole, take RETEVMO with food.
- If you take an H2 blocker (such as famotidine, nizatidine, and cimetidine), take RETEVMO 2 hours before or 10 hours after taking the H2 blocker.
- If you take an antacid that contains aluminum, magnesium, calcium, simethicone, or buffered medicines, take RETEVMO 2 hours before or 2 hours after taking the antacid.
- If you vomit after taking a dose of RETEVMO, do not take an extra dose. Take the next dose of RETEVMO at your scheduled time.
- Do not take a missed dose of RETEVMO unless it is more than 6 hours until your next scheduled dose.

What are the possible side effects of RETEVMO?

RETEVMO may cause serious side effects, including:

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

Call your healthcare provider or get emergency medical help right away if you develop any of these symptoms during treatment with RETEVMO:

- nausea
- vomiting
- weakness
- swelling
- shortness of breath
- muscle cramps
- seizures

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

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

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

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

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

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

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

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

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

How should I store RETEVMO?

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

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

General information about the safe and effective use of RETEVMO.

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

What are the ingredients in RETEVMO?

Active ingredient: selpercatinib

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

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

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

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

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This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 06/2024