

RETEVMO- selpercatinib capsule

Eli Lilly and Company

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

RETEVMO™ (selpercatinib) capsules, for oral use

Initial U.S. Approval: 2020

RECENT MAJOR CHANGES

Warnings and Precautions (5.6)

01/2021

INDICATIONS AND USAGE

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

- Adult patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC)¹ (1.1)
- Adult and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy¹ (1.2)
- Adult and pediatric patients 12 years of age and older with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)¹ (1.3)

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- **Hepatotoxicity:** Monitor ALT and AST prior to initiating RETEVMO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose, or permanently discontinue RETEVMO based on severity. (2.5, 5.1)
- **Hypertension:** Do not initiate RETEVMO in patients with uncontrolled hypertension. Optimize blood pressure (BP) prior to initiating RETEVMO. Monitor BP after 1 week, at least monthly thereafter and as clinically indicated. Withhold, reduce dose, or permanently discontinue RETEVMO based on severity. (2.5, 5.2)
- **QT Interval Prolongation:** Monitor patients who are at significant risk of developing QTc prolongation. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment. Monitor QT interval more frequently when RETEVMO is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue RETEVMO based on severity. (2.5, 5.3)
- **Hemorrhagic Events:** Permanently discontinue RETEVMO in patients with severe or life-threatening hemorrhage. (2.5, 5.4)
- **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, 5.5)
- **Tumor Lysis Syndrome:** Closely monitor patients at risk and treat as clinically indicated. (5.6)
- **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. (5.7)
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the possible risk to the fetus

and to use effective contraception. (5.8, 8.1, 8.3)

----- **ADVERSE REACTIONS** -----

The most common adverse reactions, including laboratory abnormalities, ($\geq 25\%$) were increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhea, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium, and constipation. (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)

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

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

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

Revised: 1/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

RETEVMO™ is indicated for the treatment of adult patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC).

This indication is approved under accelerated approval based on overall response rate and duration of response [see *Clinical Studies (14.1)*]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

1.2 *RET*-Mutant Medullary Thyroid Cancer

RETEVMO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy.

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

1.3 *RET* Fusion-Positive Thyroid Cancer

RETEVMO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

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

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for treatment with RETEVMO based on the presence of a *RET* gene fusion (NSCLC or thyroid cancer) or specific *RET* gene mutation (MTC) in tumor specimens or plasma [see *Clinical Studies (14)*]. An FDA-approved test for the detection of *RET* gene fusions and *RET* gene mutations is not currently available.

2.2 Important Administration Instructions

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

2.3 Recommended Dosage

The recommended dosage of RETEVMO based on body weight is:

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

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

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

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

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

2.4 Dosage Modifications for Concomitant Use of Acid-Reducing Agents

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

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

2.5 Dosage Modifications for Adverse Reactions

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

Table 1: Recommended RETEVMO Dose Reductions for Adverse Reactions

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

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

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

Table 2: Recommended RETEVMO Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Hepatotoxicity <i>[see Warnings and Precautions (5.1)]</i>	Grade 3 or Grade 4	<ul style="list-style-type: none"> • 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.
Hypertension <i>[see Warnings and Precautions (5.2)]</i>	Grade 3	<ul style="list-style-type: none"> • Withhold RETEVMO for Grade 3 hypertension that persists despite optimal antihypertensive therapy. Resume at a reduced dose when hypertension is controlled.
	Grade 4	<ul style="list-style-type: none"> • Discontinue RETEVMO.
QT Interval Prolongation <i>[see Warnings and Precautions (5.3)]</i>	Grade 3	<ul style="list-style-type: none"> • Withhold RETEVMO until recovery to baseline or Grade 0 or 1. • Resume at a reduced dose.
	Grade 4	<ul style="list-style-type: none"> • Discontinue RETEVMO
Hemorrhagic Events <i>[see Warnings and Precautions (5.4)]</i>	Grade 3 or Grade 4	<ul style="list-style-type: none"> • Withhold RETEVMO until recovery to baseline or Grade 0 or 1. • Discontinue RETEVMO for severe or life-threatening hemorrhagic events.
Hypersensitivity Reactions <i>[see Warnings and Precautions (5.5)]</i>	All Grades	<ul style="list-style-type: none"> • 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.
Other Adverse Reactions <i>[see Adverse Reactions (6.1)]</i>	Grade 3 or Grade 4	<ul style="list-style-type: none"> • Withhold RETEVMO until recovery to baseline or Grade 0 or 1. • Resume at a reduced dose.

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

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

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

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

2.7 Dosage Modification for Severe Hepatic Impairment

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

Table 4: Recommended RETEVMO Dosage for Severe Hepatic Impairment

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

3 DOSAGE FORMS AND STRENGTHS

Capsules:

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Serious hepatic adverse reactions occurred in 2.6% of patients treated with RETEVMO. Increased AST occurred in 51% of patients, including Grade 3 or 4 events in 8% and increased ALT occurred in 45% of patients, including Grade 3 or 4 events in 9% [see *Adverse Reactions (6.1)*]. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years).

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

5.2 Hypertension

Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient [see *Adverse Reactions (6.1)*]. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications.

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

5.3 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 6% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 15% of patients [see *Adverse Reactions (6.1)*]. RETEVMO has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction.

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

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

5.4 Hemorrhagic Events

Serious including fatal hemorrhagic events can occur with RETEVMO. Grade ≥ 3 hemorrhagic events occurred in 2.3% of patients treated with RETEVMO, including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis.

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

5.5 Hypersensitivity

Hypersensitivity occurred in 4.3% of patients receiving RETEVMO, including Grade 3 hypersensitivity in 1.6%. The median time to onset was 1.7 weeks (range: 6 days to 1.5 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.

5.6 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) occurred in 1% 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.

5.7 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.

5.8 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 embryoletality and malformations.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with RETEVMO and for at least 1 week after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the final dose [see *Use in Specific Populations (8.1, 8.3)*].

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

RET Gene Fusion or Gene Mutation Positive Solid Tumors

The pooled safety population described in the WARNINGS and PRECAUTIONS and below reflects exposure to RETEVMO as a single agent at 160 mg orally twice daily evaluated in 702 patients in LIBRETTO-001 [see *Clinical Studies (14)*]. Among the 702 patients who received RETEVMO, 65% were exposed for 6 months or longer and 34% were exposed for greater than one year. Among these patients, 95% 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; 52% were male; and 69% were White, 22% were Asian, 5% were Hispanic/Latino, and 3% were Black. The most common tumors were NSCLC (47%), MTC (44%), and non-medullary thyroid carcinoma (5%).

Serious adverse reactions occurred in 33% of patients who received RETEVMO. The most frequent serious adverse reaction (in $\geq 2\%$ of patients) was pneumonia. Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in > 1 patient included sepsis (n = 3), cardiac arrest (n = 3) and respiratory failure (n = 3).

Permanent discontinuation due to an adverse reaction occurred in 5% of patients who received RETEVMO. Adverse reactions resulting in permanent discontinuation included increased ALT (0.4%), sepsis (0.4%), increased AST (0.3%), drug hypersensitivity (0.3%), fatigue (0.3%), and thrombocytopenia (0.3%).

Dosage interruptions due to an adverse reaction occurred in 42% of patients who received RETEVMO. Adverse reactions requiring dosage interruption in $\geq 2\%$ of patients included ALT increased, AST increased, hypertension, diarrhea, pyrexia, and QT prolongation.

Dose reductions due to an adverse reaction occurred in 31% of patients who received RETEVMO. Adverse reactions requiring dosage reductions in $\geq 2\%$ of patients included ALT increased, AST increased, QT prolongation and fatigue.

The most common adverse reactions, including laboratory abnormalities, ($\geq 25\%$) were increased

aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhea, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium, and constipation.

Table 5 summarizes the adverse reactions in LIBRETTO-001.

Table 5: Adverse Reactions (≥ 15%) in Patients Who Received RETEVMO in LIBRETTO-001

Adverse Reaction	RETEVMO (n = 702)	
	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal		
Dry Mouth	39	0
Diarrhea ¹	37	3.4*
Constipation	25	0.6*
Nausea	23	0.6*
Abdominal pain ²	23	1.9*
Vomiting	15	0.3*
Vascular		
Hypertension	35	18
General		
Fatigue ³	35	2*
Edema ⁴	35	0.3*
Skin		
Rash ⁵	27	0.7*
Nervous System		
Headache ⁶	23	1.4*
Respiratory		
Cough ⁷	18	0
Dyspnea ⁸	16	2.3
Investigations		
Prolonged QT interval	17	4*
Blood and Lymphatic System		
Hemorrhage ⁹	15	1.9

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

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

³Fatigue includes fatigue, asthenia, malaise.

⁴Edema includes edema, edema peripheral, face edema, periorbital edema, eye edema, eyelid edema, orbital edema, localized edema, lymphedema, scrotal edema, peripheral swelling, scrotal swelling, swelling, swelling face, eye swelling.

⁵Includes rash, rash erythematous, rash macular, rash maculopapular, rash morbilliform, rash pruritic.

⁶Headache includes headache, sinus headache, tension headache.

⁷Includes cough, productive cough.

⁸Includes dyspnea, dyspnea exertional, dyspnea at rest.

⁹Hemorrhage 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, spontaneous hematoma, abdominal wall hematoma, angina bullosa hemorrhagica, diverticulum intestinal hemorrhagic, eye hemorrhage, gastrointestinal hemorrhage, gingival bleeding, hematemeses, hemorrhagic anemia, intraabdominal hemorrhage, lower

gastrointestinal hemorrhage, melena, mouth hemorrhage, occult blood positive, pelvic hematoma, periorbital hematoma, pharyngeal hemorrhage, pulmonary contusion, purpura, retroperitoneal hematoma, subarachnoid hemorrhage, subdural hemorrhage, upper gastrointestinal hemorrhage, vessel puncture site hematoma.

*Only includes a grade 3 adverse reaction.

Clinically relevant adverse reactions in ≤15% of patients who received RETEVMO include hypothyroidism and tumor lysis syndrome.

Table 6 summarizes the laboratory abnormalities in LIBRETTO-001.

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

Laboratory Abnormality	RETEVMO ¹	
	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry		
Increased AST	51	8
Increased ALT	45	9
Increased glucose	44	2.2
Decreased albumin	42	0.7
Decreased calcium	41	3.8
Increased creatinine	37	1.0
Increased alkaline phosphatase	36	2.3
Increased total cholesterol	31	0.1
Decreased sodium	27	7
Decreased magnesium	24	0.6
Increased potassium	24	1.2
Increased bilirubin	23	2.0
Decreased glucose	22	0.7
Hematology		
Decreased leukocytes	43	1.6
Decreased platelets	33	2.7

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 675 to 692 patients.

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 seliperatinib 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 (5.3)*].

Strong and Moderate CYP3A Inducers

Concomitant use of RETEVMO with a strong or moderate CYP3A inducer decreases seliperatinib 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.

7.3 Drugs that Prolong QT Interval

RETEVMO is associated with QTc interval prolongation [see *Warnings and Precautions (5.3)*, *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 seliperatinib to pregnant rats during the period of organogenesis resulted in embryoletality 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

Seliperatinib administration to pregnant rats during the period of organogenesis at oral doses \geq 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 final 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 final dose.

Males

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

Infertility

RETEVMO may impair fertility in females and males of reproductive potential [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

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

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

Animal Toxicity Data

In a 4-week general toxicology study, rats showed signs of physal hypertrophy and tooth dysplasia at doses resulting in exposures \geq approximately 3 times the human exposure at the 160 mg twice daily clinical dose. In a 13-week general toxicology study, minipigs showed signs of minimal to marked

increases in physeal thickness at the 15 mg/kg high dose level (approximately 0.3 times the human exposure at the 160 mg twice daily clinical dose). Rats in both the 4- and 13-week toxicology studies had malocclusion and tooth discoloration at the high dose levels (≥ 1.5 times the human exposure at the 160 mg twice daily clinical dose) that persisted during the recovery period.

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

8.5 Geriatric Use

Of 702 patients who received RETEVMO, 34% (239 patients) were ≥ 65 years of age and 10% (67 patients) were ≥ 75 years of age. No overall differences were observed in the safety or effectiveness of RETEVMO between patients who were ≥ 65 years of age and younger patients.

8.6 Renal Impairment

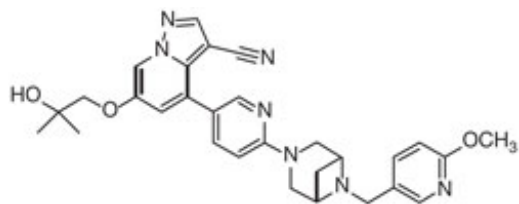
No dosage modification is recommended for patients with mild to severe renal impairment [estimated Glomerular Filtration Rate (eGFR) ≥ 15 to 89 mL/min, estimated by Modification of Diet in Renal Disease (MDRD) equation]. The recommended dosage has not been established for patients with end-stage renal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

8.7 Hepatic Impairment

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

11 DESCRIPTION

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



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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Selpercatinib is a kinase inhibitor. Selpercatinib inhibited wild-type RET and multiple mutated RET isoforms as well as VEGFR1 and VEGFR3 with IC₅₀ values ranging from 0.92 nM to 67.8 nM. In other enzyme assays, selpercatinib also inhibited FGFR 1, 2, and 3 at higher concentrations that were still clinically achievable. In cellular assays, selpercatinib inhibited RET at approximately 60-fold lower concentrations than FGFR1 and 2 and approximately 8-fold lower concentration than VEGFR3.

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

12.2 Pharmacodynamics

Exposure-Response Relationship

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

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

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

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

Absorption

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

Effect of Food

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

Distribution

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

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

Elimination

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

Metabolism

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

Excretion

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

Specific Populations

The apparent volume of distribution and clearance of selpercatinib increase with increasing body weight (27 kg to 177 kg).

No clinically significant differences in the pharmacokinetics of selpercatinib were observed based on age (15 years to 90 years), sex, or mild, moderate, or severe renal impairment (eGFR \geq 15 to 89 mL/min). The effect of ESRD on selpercatinib pharmacokinetics has not been studied.

Patients with Hepatic Impairment

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

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

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

Table 7: Change in Selpercatinib Exposure After Coadministration with PPI

	Selpercatinib AUC_{0-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 1000 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-INF} by 133% and C_{max} by 30%.

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

Strong CYP3A Inducers: Coadministration of multiple doses of rifampin (strong CYP3A inducer) decreased the selpercatinib AUC_{0-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-INF} by 188% and C_{max} by 91%.

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

P-glycoprotein (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, P-gp, 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 Metastatic *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 advanced 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), or fluorescence in situ hybridization (FISH). 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.

Metastatic *RET* Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy

Efficacy was evaluated in 105 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); 59% were female; 52% were White, 38% were Asian, 4.8% were Black, and 3.8% were Hispanic/Latino. ECOG performance status was 0-1 (98%) or 2 (2%) and 98% of patients had metastatic disease. Patients received a median of 3 prior systemic therapies (range 1–15); 55% had prior anti-PD-1/PD-L1 therapy. *RET* fusions were detected in 90% of patients using NGS (81.9% tumor samples; 7.6% blood or plasma samples), 8.6% using FISH, and 1.9% using PCR.

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

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

	RETEVMO (n = 105)
Overall Response Rate¹ (95% CI)	64% (54%, 73%)
Complete response	1.9%
Partial response	62%
Duration of Response	
Median in months (95% CI)	17.5 (12, NE)
% with ≥ 6 months ²	81

¹ Confirmed overall response rate assessed by BICR.

² Based on observed duration of response

NE = not estimable

For the 58 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 66% (95% CI: 52%, 78%) and the median DOR was not reached (95% CI: 12.0, NE).

Among the 105 patients with *RET* fusion-positive NSCLC, 11 had measurable CNS metastases at baseline as assessed by BIRC. No patients received radiation therapy (RT) to the brain within 2 months prior to study entry. Responses in intracranial lesions were observed in 10 of these 11 patients; all responders had a DOR of ≥ 6 months.

Treatment-naïve *RET* Fusion-Positive NSCLC

Efficacy was evaluated in 39 patients with treatment-naïve *RET* fusion-positive NSCLC enrolled into a cohort of LIBRETTO-001.

The median age was 61 years (range 23 to 86); 56% were female; 72% were White, 18% were Asian, and 8% were Black. ECOG performance status was 0-1 in all patients (100%) and all patients (100%) had metastatic disease. *RET* fusions were detected in 92% of patients using NGS (69% tumor samples; 23% in blood) and 8% using FISH.

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

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

	RETEVMO (n =39)
Overall Response Rate¹ (95% CI)	85% (70%, 94%)
Complete response	0
Partial response	85%
Duration of Response	
Median in months (95% CI)	NE (12, NE)
% with ≥ 6 months ²	58

¹ Confirmed overall response rate assessed by BICR.

² Based on observed duration of response

NE = not estimable

14.2 *RET*-Mutant Medullary Thyroid Cancer

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

RET-Mutant MTC Previously Treated with Cabozantinib or Vandetanib

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

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

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

RET Mutation Type¹	Previously Treated (n = 55)	Cabozantinib/ Vandetanib Naïve (n = 88)	Total (n = 143)
M918T	33	49	82
Extracellular cysteine mutation ²	7	20	27
V804M or V804L	5 ⁴	6	11
Other ³	10	13	23

¹ Somatic or germline mutations; protein change.

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

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

⁴ One patient also had a M918T mutation

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

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

	RETEVMO (n = 55)
Overall Response Rate¹ (95% CI)	69% (55%, 81%)
Complete response	9%
Partial response	60%
Duration of Response	
Median in months (95% CI)	NE (19.1, NE)
% with \geq 6 months ²	76

¹ Confirmed overall response rate assessed by BICR.

² Based on observed duration of response

NE = not estimable

Cabozantinib and Vandetanib-naïve *RET*-Mutant MTC

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

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

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

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

	RETEVMO (n = 88)
Overall Response Rate¹ (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 BICR.

² Based on observed duration of response

NE = not estimable

14.3 RET Fusion-Positive Thyroid Cancer

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

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

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

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

	RETEVMO Previously Treated (n = 19)	RETEVMO Systemic Therapy Naïve (n = 8)
Overall Response Rate¹ (95% CI)	79% (54%, 94%)	100% (63%, 100%)
Complete response	5.3%	12.5%
Partial response	74%	88%
Duration of Response		
Median in months (95% CI)	18.4 (7.6, NE)	NE (NE, NE)
% with ≥ 6 months ²	87	75

¹ Confirmed overall response rate assessed by BICR.

² Based on observed duration of response

NE = not estimable

16 HOW SUPPLIED/STORAGE AND HANDLING

RETEVMO (selpercatinib) capsules are supplied as follows:

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

- 60 count bottle NDC 0002-3977-60

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

- 60 count bottle NDC 0002-2980-60

- 120 count bottle NDC 0002-2980-26

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

17 PATIENT COUNSELING INFORMATION

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

Hepatotoxicity

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

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 (5.2)*].

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 (5.3)*].

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 (5.4)*].

Hypersensitivity Reactions

Advise patients to monitor for signs and symptoms of hypersensitivity reactions, particularly during the first month of treatment [see *Warnings and Precautions (5.5)*].

Tumor Lysis Syndrome

Advise patients to contact their healthcare provider promptly to report any signs and symptoms of TLS [see *Warnings and Precautions (5.6)*].

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 (5.7)*].

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 (5.8), Use in Specific Populations (8.1)*].

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

Lactation

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

Infertility

Advise males and females of reproductive potential that RETEVMO may impair fertility [see *Nonclinical Toxicology (13.1)*].

Drug Interactions

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

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

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RET-0002-USPI-20210128

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

What is RETEVMO?

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

- adults with non-small cell lung cancer (NSCLC) that has spread.
- adults and children 12 years of age and older with advanced medullary thyroid cancer (MTC) or MTC that has spread who require a medicine by mouth or injection (systemic therapy).
- adults and children 12 years of age and older with advanced thyroid cancer or thyroid cancer that has spread who require a medicine by mouth or injection (systemic therapy) and who have received radioactive iodine and it did not work or is no longer working.

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 in children younger than 12 years of age.

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

- have liver problems
- 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 at least **1 week** after the final 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 at least **1 week** after the final 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 the last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Certain other medicines may affect how RETEVMO works.

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

How should I take RETEVMO?

- Take RETEVMO exactly as your healthcare provider tells you.
- Your healthcare provider may stop treatment or change your dose of RETEVMO if you have side effects. Do not change your dose or stop taking RETEVMO unless your healthcare provider tells you.
- RETEVMO is taken by mouth, usually 2 times a day 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.
- RETEVMO doses should be separated by 12 hours.
- If you take an antacid that contains aluminum, magnesium, calcium, simethicone, or buffered medicines, take RETEVMO 2 hours before or 2 hours after taking the antacid.
- If you take an H2 blocker (such as famotidine, nizatidine, and cimetidine), take RETEVMO 2 hours before or 10 hours after taking the H2 blocker.
- Swallow RETEVMO capsules whole. Do not chew or crush the capsules.
- If you vomit after taking a dose of RETEVMO, do not take an extra dose. Take the next dose of RETEVMO at your scheduled time.
- Do not take a missed dose of RETEVMO unless it is more than 6 hours until your next scheduled dose.
- If you take too much RETEVMO, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of RETEVMO?

RETEVMO may cause serious side effects, including:

- **Liver problems.** Liver problems (increased liver enzymes) are common with RETEVMO and may sometimes be serious. Your healthcare provider will do blood tests before and during treatment with RETEVMO to check for liver problems. Tell your healthcare provider right away if you get any of the following symptoms of liver problems during treatment:
 - yellowing of your skin or the white part of your eyes (jaundice)
 - dark “tea-colored” urine
 - sleepiness
 - bleeding or bruising
 - loss of appetite
 - nausea or vomiting
 - pain on the upper right side of your stomach area

Your healthcare provider may temporarily stop treatment, lower your dose, or permanently stop

RETEVMO if you develop liver problems with RETEVMO

- **High blood pressure (hypertension).** High blood pressure is common with RETEVMO and may sometimes be serious. You should check your blood pressure regularly during treatment with RETEVMO. Tell your healthcare provider if you get any of the following symptoms:
 - confusion
 - dizziness
 - headaches
 - chest pain
 - shortness of breath
- **Heart rhythm changes (QT prolongation)** can occur and may be serious. RETEVMO may cause very slow, very fast or irregular heartbeats. Tell your healthcare provider right away if you get any of the following symptoms:
 - loss of consciousness
 - dizziness
 - fainting
 - 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
 - unusual vaginal bleeding
 - pink or brown urine
 - nose bleeds that happen often
 - red or black (looks like tar) stools
 - drowsiness or difficulty being awakened
 - coughing up blood or blood clots
 - confusion
 - headache
 - unusual bleeding or bruising of your skin
 - change in speech
 - menstrual bleeding that is heavier than normal
- **Allergic reactions.** RETEVMO can cause a fever, rash, muscle or joint pain, especially in the first month of treatment. Tell your healthcare provider if you get any of these symptoms. Your healthcare provider may temporarily stop treatment or lower your dose of RETEVMO.
- **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
 - shortness of breath
 - vomiting
 - muscle cramps
 - weakness
 - seizures
 - swelling
- **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.

The most common side effects of RETEVMO include:

- increased levels of liver enzymes
- increased blood sugar levels
- decrease in white blood cell count
- decreased protein levels (albumin) in the blood
- decreased levels of calcium in the blood
- dry mouth
- diarrhea
- increased creatinine (kidney function test)
- high blood pressure
- tiredness
- swelling of your arms, legs, hands, and feet (peripheral edema)
- decrease in platelet count
- increased cholesterol levels
- rash
- decreased levels of salt (sodium) in the blood
- constipation

RETEVMO may affect fertility in females and males, which may affect your ability to have children. Talk to your healthcare provider if this is a concern for you. These are not all the possible side effects with RETEVMO. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store RETEVMO?

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

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

General information about the safe and effective use of RETEVMO.

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

What are the ingredients in RETEVMO?

Active ingredient: selpercatinib

Inactive ingredients: microcrystalline cellulose, colloidal silicon dioxide

Capsule: gelatin, titanium dioxide and edible ink

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

RET-0002-PPI-20210128

For more information, go to www.RETEVMO.com or call 1-800-545-5979

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: 01/2021

PACKAGE LABEL - Retevmo 40 mg 60 Count Bottle

Retevmo 40 mg Bottle

NDC-0002-3977-60

60 capsules

Rx only

Retevmo™

(selpercatinib)

capsules

40 mg

Each capsule contains 40 mg selpercatinib

www.retevmo.com

Lilly



PACKAGE LABEL - Retevmo 80 mg 60 Count Bottle

NDC-0002-2980-60

Rx only

Retevmo™

(selpercatinib)

capsules

80 mg

Each capsule contains 80 mg selpercatinib

www.retevmo.com

Lilly



RETEVMO

selpercatinib capsule

Product Information

Product Type

HUMAN PRESCRIPTION DRUG

Item Code (Source)

NDC:0002-3977

Route of Administration	ORAL			
Active Ingredient/Active Moiety				
	Ingredient Name	Basis of Strength	Strength	
	selpercatinib (UNII: CEGM9 YBNGD) (selpercatinib - UNII:CEGM9 YBNGD)	selpercatinib	40 mg	
Inactive Ingredients				
	Ingredient Name	Strength		
	microcrystalline cellulose (UNII: OP1R32D61U)			
	silicon dioxide (UNII: ETJ7Z6XBU4)			
	gelatin, unspecified (UNII: 2G86QN327L)			
	titanium dioxide (UNII: 15FIX9V2JP)			
	ferrosoferric oxide (UNII: XM0M87F357)			
	shellac (UNII: 46N107B71O)			
	alcohol (UNII: 3K9958V90M)			
	isopropyl alcohol (UNII: ND2M416302)			
	butyl alcohol (UNII: 8PJ61P6TS3)			
	propylene glycol (UNII: 6DC9Q167V3)			
	water (UNII: 059QF0K00R)			
	ammonia (UNII: 5138Q19F1X)			
	potassium hydroxide (UNII: WZHBC48M4T)			
Product Characteristics				
Color	GRAY (Gray Opaque)	Score	no score	
Shape	CAPSULE	Size	18mm	
Flavor		Imprint Code	Lilly;3977;40mg	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0002-3977-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	05/08/2020	
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
NDA	NDA213246	05/08/2020		

RETEVMO			
selpercatinib capsule			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0002-2980

Route of Administration	ORAL			
Active Ingredient/Active Moiety				
	Ingredient Name	Basis of Strength	Strength	
	selpercatinib (UNII: CEGM9 YBNGD) (selpercatinib - UNII:CEGM9 YBNGD)	selpercatinib	80 mg	
Inactive Ingredients				
	Ingredient Name	Strength		
	microcrystalline cellulose (UNII: OP1R32D61U)			
	silicon dioxide (UNII: ETJ7Z6XBU4)			
	gelatin, unspecified (UNII: 2G86QN327L)			
	titanium dioxide (UNII: 15FIX9V2JP)			
	FD&C Blue No. 1 (UNII: H3R47K3TBD)			
	shellac (UNII: 46N107B71O)			
	alcohol (UNII: 3K9958V90M)			
	isopropyl alcohol (UNII: ND2M416302)			
	butyl alcohol (UNII: 8PJ61P6TS3)			
	propylene glycol (UNII: 6DC9Q167V3)			
	water (UNII: 059QF0KO0R)			
	ammonia (UNII: 5138Q19F1X)			
	potassium hydroxide (UNII: WZHBC48M4T)			
	ferrosoferric oxide (UNII: XM0M87F357)			
Product Characteristics				
Color	BLUE (Blue Opaque)	Score	no score	
Shape	CAPSULE	Size	22mm	
Flavor		Imprint Code	Lilly;2980;80mg	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0002-2980-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	05/08/2020	
2	NDC:0002-2980-26	120 in 1 BOTTLE; Type 0: Not a Combination Product	05/08/2020	
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
NDA	NDA213246	05/08/2020		

Labeler - Eli Lilly and Company (006421325)

Registrant - Loxo Oncology, Inc. (042572897)

